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Laparoscopic versus open gastrectomy for gastric cancer (Review)

Best LMJ, Mughal M, Gurusamy KS

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[Intervention Review]

Laparoscopic versus open gastrectomy for gastric cancer

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ABSTRACT

Background

Gastric cancer is the third most common cause of cancer-related mortality in the world. Currently there are two surgical options for potentially curable patients (i.e. people with non-metastatic gastric cancer), laparoscopic and open gastrectomy. However, it is not clear whether one of these options is superior.

Objectives

To assess the benefits and harms of laparoscopic gastrectomy or laparoscopy-assisted gastrectomy versus open gastrectomy for people with gastric cancer. In particular, we planned to investigate the effects by patient groups, such as cancer stage, anaesthetic risk, and body mass index (BMI), and by intervention methods, such as method of anastomosis, type of gastrectomy and laparoscopic or laparoscopically-assisted gastrectomy.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Science Citation Index, ClinicalTrials.gov and the WHO ICTRP (World Health Organization International Clinical Trials Registry Platform) until September 2015. We also screened reference lists from included trials.

Selection criteria

Two review authors independently selected references for further assessment by going through all titles and abstracts. Further selection was based on review of full text articles for selected references.

Data collection and analysis

Two review authors independently extracted study data. We calculated the risk ratio (RR) with 95% confidence interval (CI) for binary outcomes, the mean difference (MD) or the standardised mean difference (SMD) with 95% CI for continuous outcomes and the hazard ratio (HR) for time-to-event outcomes. We performed meta-analyses where it was meaningful.

Main results

In total, 2794 participants were randomised in 13 trials included in this review. All the trials were at unclear or high risk of bias. One trial (which included 53 participants) did not contribute any data to this review. A total of 213 participants were excluded in the remaining trials after randomisation, leaving a total of 2528 randomised participants for analysis, with 1288 undergoing laparoscopic gastrectomy and 1240 undergoing open gastrectomy. All the participants were suitable for major surgery.

There was no difference in the proportion of participants who died within thirty days of treatment between laparoscopic gastrectomy (7/1188: adjusted proportion = 0.6% (based on meta-analysis)) and open gastrectomy (4/1447: 0.3%) (RR 1.60, 95% CI 0.50 to 5.10; risk

difference 0.00, 95% CI -0.01 to 0.01; participants = 2335; studies = 11; I^2 = 0%; low quality evidence). There were no events in either group for short-term recurrence (participants = 103; studies = 3), proportion requiring blood transfusion (participants = 66; studies = 2), and proportion with positive margins at histopathology (participants = 28; studies = 1). None of the trials reported health-related quality of life, time to return to normal activity or time to return to work. The differences in long-term mortality (HR 0.94, 95% CI 0.70 to 1.25; participants = 195; studies = 3; I^2 = 0%; very low quality evidence), serious adverse events within three months (laparoscopic gastrectomy (7/216: adjusted proportion = 3.6%) versus open gastrectomy (13/216: 6%) (RR 0.60, 95% CI 0.27 to 1.34; participants = 432; studies = 8; I^2 = 0%; very low quality evidence), long-term recurrence (HR 0.95, 95% CI 0.70 to 1.30; participants = 162; studies = 4; very low quality evidence), adverse events within three months (laparoscopic gastrectomy (204/268: adjusted proportion = 16.1%) versus open gastrectomy (253/1222: 20.7%) (RR 0.78, 95% CI 0.60 to 1.01; participants = 2490; studies = 11; I^2 = 38%; very low quality evidence), quantity of perioperative blood transfused (SMD 0.05, 95% CI -0.27 to 0.38; participants = 143; studies = 2; I^2 = 0%; very low quality evidence), length of hospital stay (MD -1.82 days, 95% CI -3.72 to 0.07; participants = 319; studies = 6; I^2 = 83%; very low quality evidence), and number of lymph nodes harvested (MD -0.63, 95% CI -1.51 to 0.25; participants = 472; studies = 9; I^2 = 40%; very low quality evidence) were imprecise. There was no alteration in the interpretation of the results in any of the subgroups.

Authors' conclusions

Based on low quality evidence, there is no difference in short-term mortality between laparoscopic and open gastrectomy. Based on very low quality evidence, there is no evidence for any differences in short-term or long-term outcomes between laparoscopic and open gastrectomy. However, the data are sparse, and the confidence intervals were wide, suggesting that significant benefits or harms of laparoscopic gastrectomy cannot be ruled out. Several trials are currently being conducted and interim results of these trials have been included in this review. These trials need to perform intention-to-treat analysis to ensure that the results are reliable and report the results according to the CONSORT Statement.

PLAIN LANGUAGE SUMMARY

Laparoscopic (key hole) operation versus open operation for treatment of people with stomach cancer

Review question

Is laparoscopic treatment (key hole surgery) equivalent to open surgical treatment for treatment of people with gastric (stomach) cancer?

Background

Stomach cancer is the third most frequent cause of cancer-related death in the world. If cancer has not spread to other areas of the body, and if the person can withstand a major operation, depending upon the part of the stomach involved, removal of part of the stomach, or the entire stomach (gastrectomy), is the only treatment that offers long-term cure of cancer. Gastrectomy can be performed by laparoscopic (key hole) operation, or by open operation, which involves a large cut. While the cut is smaller with key hole surgery, it is not clear whether key hole surgery is as safe as open surgery, and whether it offers any advantages in terms of quicker recovery of people undergoing gastrectomy. We sought to resolve this issue by searching the medical literature for studies reported until September 2015 that compared laparoscopic and open gastrectomy in people with stomach cancer.

Study characteristics

We identified 13 eligible studies (2794 participants) for this review. One trial did not report any information that we sought. Information on 213 participants was not reported because of various reasons, the common reason being that they did not receive the planned treatment. A total of 2528 participants received either laparoscopic gastrectomy (1288 participants) or open gastrectomy (1240 participants). The decision on whether a participant received laparoscopic or open gastrectomy was made using methods similar to the toss of a coin. This process ensures that the participants in the two groups are similar. All the participants were suitable for major surgery.

Key results

There was no difference between laparoscopic and open gastrectomy in short-term deaths (laparoscopic gastrectomy: 6 deaths in 1000 operations versus open gastrectomy: 3 deaths in 1000 operations). There is a certain amount of uncertainty when predicting the number of deaths or outcomes based on information in the trials. Because of this uncertainty, we were able to conclude that there was no difference in short-term deaths between the groups, although the deaths in laparoscopic gastrectomy was twice that in open gastrectomy. None of the trials reported health-related quality of life, time to return to normal activity or time to return to work. The differences in long-term deaths, serious complications within three months (laparoscopic gastrectomy: 36 complications per 1000 operations versus open gastrectomy: 60 complications per 1000 operations), all complications within three months (laparoscopic gastrectomy: 161 complications per 1000 operations versus open gastrectomy: 253 complications in 1000 operations, short-term and long-term recurrence of cancer, number of people who required blood transfusion, amount of blood transfused during or within one week of surgery, and length of hospital stay were imprecise. As a result, significant benefits or harms of laparoscopic gastrectomy compared to open gastrectomy cannot be ruled out. Further well designed trials are necessary to compare the benefits and harms of laparoscopic and open gastrectomy.

Quality of the evidence

The quality of evidence was very low for all outcomes, apart from short-term mortality, which was low. As a result, there is a lot of uncertainty regarding the results.

Summary of findings for the main comparison. Laparoscopic gastrectomy compared to open gastrectomy for gastric cancer (primary outcomes)

Laparoscopic gastrectomy compared to open gastrectomy for gastric cancer (primary outcomes)

Patient or population: patients with gastric cancer
Settings: secondary or tertiary setting
Intervention: laparoscopic gastrectomy
Comparison: open gastrectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Open gastrectomy	Laparoscopic gastrectomy			
Short-term mortality	**3 per 1000**	**6 per 1000** (2 to 18)	**RR 1.60** (0.50 to 5.10)	2335 (11 studies)	⊕⊕⊖⊖ **low** [1]
Long-term mortality (maximal follow-up)	**448 per 1000**	**428 per 1000** (340 to 524)	**HR 0.94** (0.70 to 1.25)	195 (3 studies)	⊕⊖⊖⊖ **very low** [1,2]
Proportion with a serious adverse event (< 3 months)	**60 per 1000**	**36 per 1000** (16 to 81)	**RR 0.60** (0.27 to 1.34)	432 (8 studies)	⊕⊖⊖⊖ **very low** [1,2]

Health-related quality of life during short-term (four weeks to three months) or medium-term (more than three months to one year) was not reported.

*The basis for the **assumed risk** was the mean control group proportion. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] There was unclear or high risk bias within the trials (downgraded by two levels).
[2] The confidence intervals were wide (overlaps no effect and clinically significantly effect) and the sample size was small (downgraded by two levels).

Summary of findings 2. Laparoscopic gastrectomy compared to open gastrectomy for gastric cancer (secondary outcomes)

Laparoscopic gastrectomy compared to open gastrectomy for gastric cancer (secondary outcomes)

Patient or population: patients with gastric cancer
Settings: secondary or tertiary setting
Intervention: laparoscopic gastrectomy
Comparison: open gastrectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Open gastrectomy	Laparoscopic gastrectomy				
Long-term recurrence (maximal follow-up)	**450 per 1000**	**433 per 1000** (342 to 540)	**HR 0.95** (0.70 to 1.30)	162 (4 studies)	⊕⊖⊖⊖ **very low** [1,2]	
Proportion with an adverse event (< 3 months)	**207 per 1000**	**161 per 1000** (124 to 209)	**RR 0.78** (0.60 to 1.01)	2490 (11 studies)	⊕⊖⊖⊖ **very low** [1,3]	
Quantity of perioperative blood transfused	The mean quantity of perioperative blood transfused in the control groups was **0.08 litres**	The mean quantity of perioperative blood transfused in the intervention groups was **0.05 standard deviations higher** (0.27 lower to 0.38 higher)		143 (2 studies)	⊕⊖⊖⊖ **very low** [1,2]	SMD 0.05 (-0.27 to 0.38)
Length of hospital stay		The mean length of hospital stay in the intervention groups was **1.82 lower** (3.72 lower to 0.07 higher)		319 (6 studies)	⊕⊖⊖⊖ **very low** [1,2,4]	
Number of lymph nodes harvested	The mean number of lymph nodes harvested in the control groups was **27**	The mean number of lymph nodes harvested in the intervention groups was **0.63 lower** (1.51 lower to 0.25 higher)		472 (9 studies)	⊕⊖⊖⊖ **very low** [1,4]	

There were no events in either group for short-term recurrence (103 participants (3 studies)), proportion requiring blood transfusion (66 participants (2 studies)), proportion with positive resection margin (incomplete cancer resection) (14 participants (1 study)).

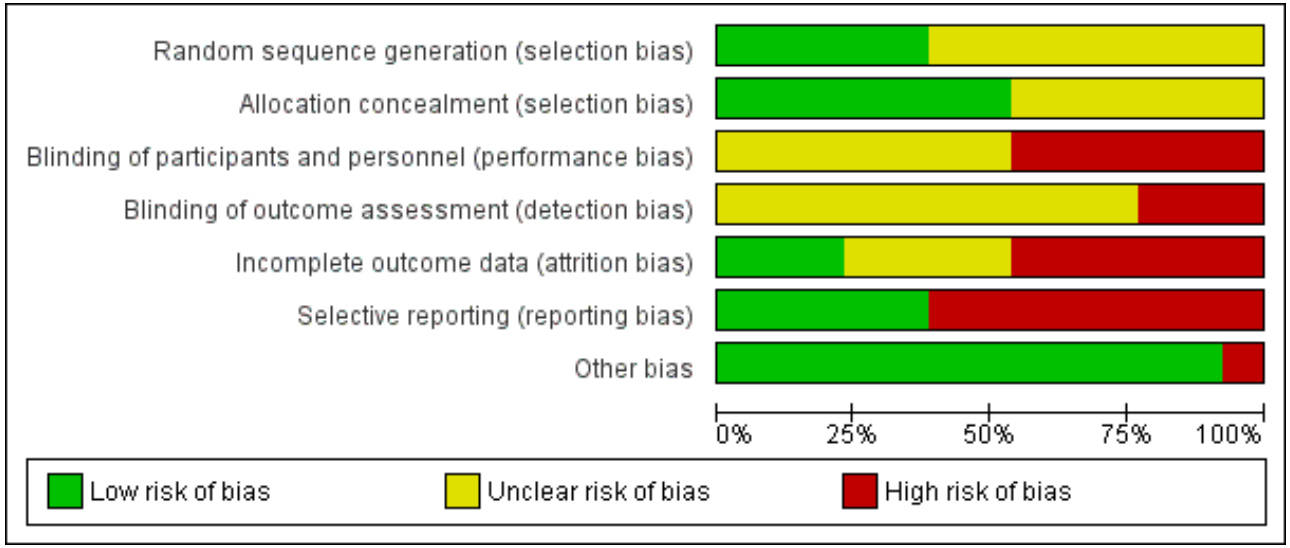
None of the trials reported on measures of earlier postoperative recovery such as time to return to normal activity or time to return to work.

*The basis for the **assumed risk** was the mean control group proportion. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; HR: hazard ratio; **RR:** risk ratio; **SMD:** standardised mean difference.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] There was unclear or high risk of bias within the trials (downgraded by two levels). Please see Figure 1 and Figure 2 which show this.
[2] The confidence intervals were wide (overlaps no effect and clinically significantly effect) and the sample size was small (downgraded by two levels).
[3] Visual inspection revealed that studies with large variance were more in the favour of laparoscopic group than the open group, suggesting potential reporting bias (downgraded by one level).
[4] Significant heterogeneity detected in the studies by the I^2 values and Chi^2 test (downgraded by two levels).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



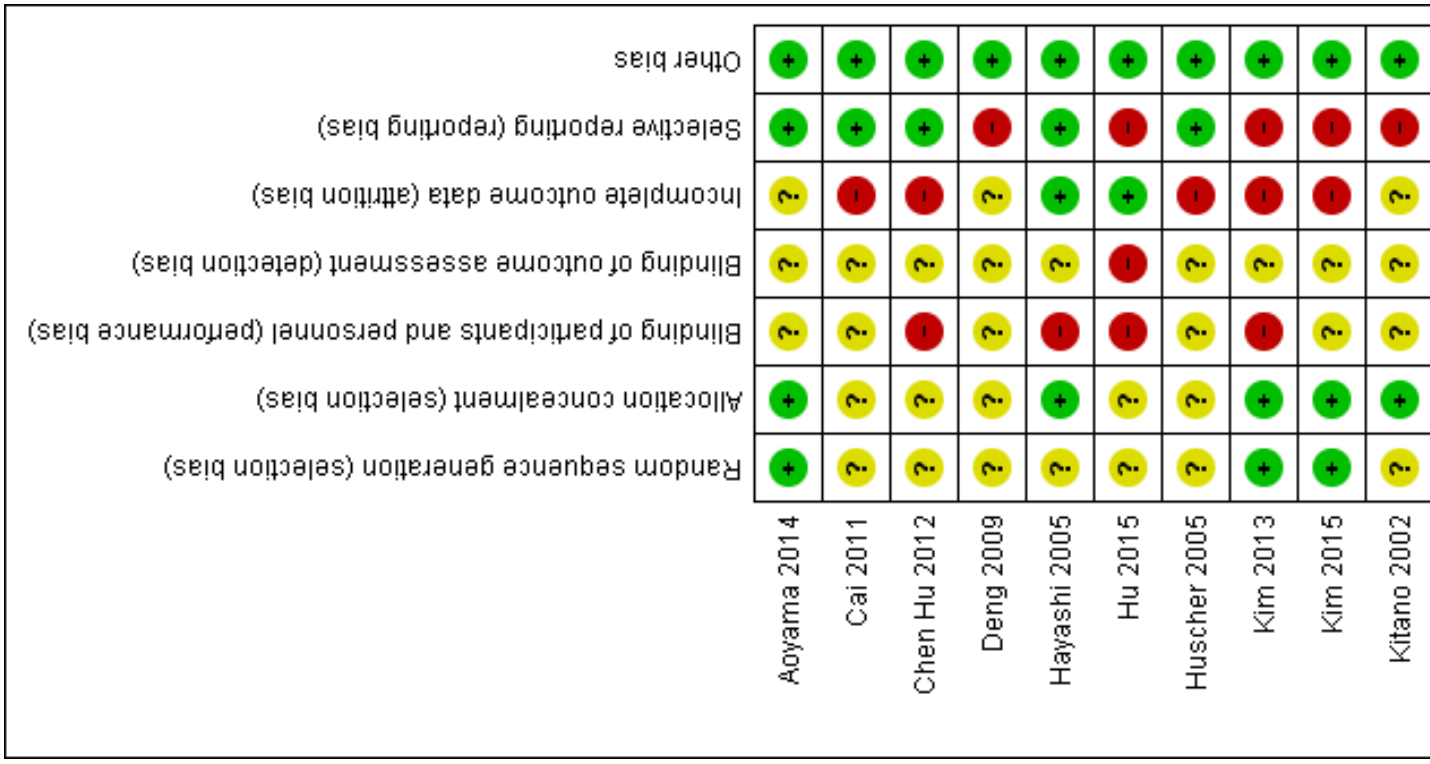


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

BACKGROUND

Description of the condition

Adenocarcinoma of the stomach (or stomach cancer) is the fifth most common cancer and the third most common cause of cancer-related mortality in the world (IARC 2014). In 2012, there were about 950,000 newly diagnosed cases of gastric cancer and 725,000 deaths due to gastric cancer globally (IARC 2014). There is global variation in the incidence of gastric cancers with an age-standardised annual incidence rate of 30 to 42 per 100,000 population in East Asian countries such as Japan, Mongolia, and Korea compared with an age-standardised annual incidence rate of 1 to 5 per 100,000 population in Africa, Australia, the USA, and the UK (IARC 2014). The trend in mortality is different. For example, the age-standardised annual mortality rate in Mongolia is 25 per 100,000 population compared with 13 per 100,000 population in Korea and Japan despite a higher age-standardised annual incidence in Korea than Mongolia (IARC 2014).

There is a decreasing trend in the overall incidence of gastric cancers, possibly due to lifestyle changes, such as decreased consumption of salted and preserved foods, increased consumption of fruits and vegetables, decreased smoking and reduction of*Helicobacter pylori (H. pylori)* (Cancer Research UK 2014; Jemal 2010).

The treatment of gastric cancer depends upon the stage of cancer. One of the common systems for staging cancer currently is the American Joint Committee on Cancer (AJCC) gastric cancer staging system - AJCC 7th edition (AJCC 2010; Washington 2010). This system is based on the involvement of the different layers of the stomach by the tumour (T), nodal involvement (N), and the presence of metastases (M) (TNM classification). Early gastric cancer is cancer that is confined to the submucosa (T1) with or without nodal involvement, although this definition of early gastric cancer has been challenged since nodal status is an important prognostic factor in survival (Inoue 1991; Kim 1995). If the cancer has penetrated beyond the submucosa, it is called advanced gastric cancer. Metastatic gastric cancer corresponds to Stage IV of the AJCC gastric cancer staging system. The survival after diagnosis of gastric cancer depends upon the stage with five-year survival ranging from 70% in Stage Ia cancer to 5% in Stage IV cancer (AJCC 2010; Washington 2010). The treatment of gastric cancer depends upon the stage of the disease. Potentially curative treatment is possible for stages I to III (Japanese Gastric Cancer Association 2011; Waddell 2013). Apart from $T_{1a}N_0M_0$ stage, where endoscopic treatment may be performed, and stage IV, where palliative treatment is recommended, the remaining stages are treated by resection of the stomach (gastrectomy) (Bennett 2009; Japanese Gastric Cancer Association 2011; Waddell 2013).

Description of the intervention

In open gastrectomy, the surgical access to the abdominal cavity (and hence the stomach) is by upper midline incision, a bilateral subcostal incision (roof-top or Chevron incision), or a transverse abdominal incision (Inaba 2004; Stuart 1997). In laparoscopy-assisted gastrectomy, the surgical access to the abdominal cavity (and hence the stomach) is by a small abdominal incision (about 5 cm) and additional five or six small ports (holes) of about 0.5 cm to 1 cm each through which laparoscopic instruments can be inserted after the abdomen is distended using carbon dioxide pneumoperitoneum. Part of the surgery, usually the anastomosis restoring the continuity of the gastrointestinal tract, is performed outside the body (extracorporeal) (Lee 2013). The resected stomach is removed through the small abdominal incision. In totally laparoscopic gastrectomy, the surgical access to the abdominal cavity (and hence the stomach) is only by five or six small ports of about 0.5 to 1 cm each through which laparoscopic instruments can be inserted after the abdomen is distended using carbon dioxide pneumoperitoneum. The entire surgery is performed laparoscopically (Zhang 2015).

The standard operations are total gastrectomy and subtotal gastrectomy, and are recommended in the presence of nodal involvement or T_2 to T_{4a} tumours. Subtotal gastrectomy can be performed when a minimum of 2 to 5 cm proximal cancer-free margin can be achieved, depending upon the depth of infiltration and the growth pattern of the cancer (Japanese Gastric Cancer Association 2011). Proximal gastrectomy can be performed for T_1N_0 proximal gastric cancers when more than half of the distal stomach can be preserved; and a pylorus-preserving gastrectomy can be performed for T_1N_0 cancers of the middle third of the stomach when the distal margin of the tumour is at least 4 cm from the pylorus (Japanese Gastric Cancer Association 2011). The extent of lymph node excision, and the method of restoration of continuity of the gastrointestinal tract, are controversial (Japanese Gastric Cancer Association 2011; Memon 2011; Waddell 2013; Xiong 2013). Postoperative chemotherapy is recommended after gastrectomy for resectable gastric cancer (Diaz-Nieto 2013; Waddell 2013).

How the intervention might work

For many surgical procedures, laparoscopic surgery is currently preferred over open surgery. This includes surgical procedures such as cholecystectomy (removal of gallbladder), colon cancer, and hysterectomy (Bijen 2009; Keus 2006; Reza 2006; Talseth 2014; Walsh 2009). The reason for this preference of laparoscopic surgery over open surgery is because of decreased pain, decreased blood loss, shorter hospital stay, earlier postoperative recovery, better cosmesis (physical appearance), and decreased costs (Bijen 2009; Keus 2006; Reza 2006; Talseth 2014; Walsh 2009).

Why it is important to do this review

While the smaller incision and earlier postoperative recovery appear to be potential advantages of laparoscopic gastrectomy or laparoscopy-assisted gastrectomy, the safety of the laparoscopic approach (for a procedure that has a high complication rate) and cancer clearance after laparoscopic and laparoscopy-assisted gastrectomy has to be ensured before the method can be widely recommended. There are concerns about cancer clearance, since port site metastases (recurrence of cancer at the laparoscopic port site) have been reported after many cancers (Kais 2014; Palomba 2014; Song 2014). Animal research has shown that the increased intra-abdominal pressure during laparoscopy (pneumoperitoneum) may drive the malignant cells into ports, resulting in seeding of the port site and port site metastases (Hopkins 1999). Another reason is that the malignant cells may be adherent to the laparoscopic instruments that are introduced and removed through the ports, resulting in seeding of the port site and port site metastases (Hopkins 1999). Another issue is the adequacy of cancer clearance in terms of resection margins and the extent of lymph nodes removed with laparoscopy. Therefore, oncological safety (cancer clearance) is an important issue with

laparoscopic and laparoscopic-assisted gastrectomy. There is no Cochrane review on this topic.

OBJECTIVES

To assess the benefits and harms of laparoscopic gastrectomy or laparoscopy-assisted gastrectomy versus open gastrectomy for people with gastric cancer. In particular, we planned to investigate the effects by patient groups, such as cancer stage, anaesthetic risk, and body mass index (BMI), and by intervention methods, such as method of anastomosis, type of gastrectomy and laparoscopic or laparoscopically-assisted gastrectomy.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs). We included studies reported as full text, studies published as abstract only, and unpublished data.

Types of participants

We included adults undergoing gastrectomy for gastric adenocarcinoma (cancer). We included trials in which separate outcome data for people undergoing gastrectomy for gastric adenocarcinoma were available, even if some of the participants underwent gastrectomy for other causes, including lymphomas.

Types of interventions

We included trials comparing laparoscopic gastrectomy or laparoscopy-assisted gastrectomy with open gastrectomy, provided that the only difference between the randomised groups was the use of laparoscopic (or laparoscopy-assisted) or open method of access to the stomach. We excluded trials comparing totally laparoscopic gastrectomy with laparoscopy-assisted gastrectomy or different methods of open or laparoscopic gastrectomy. We also excluded any trials comparing robot-assisted gastrectomy with laparoscopic or open gastrectomy.

Types of outcome measures

Primary outcomes

1. Mortality
   a. Short-term mortality (in-hospital mortality or mortality within three months)
   b. Long-term mortality (at maximal follow-up)
2. Serious adverse events (within three months). We accepted the following definitions of serious adverse events.
   a. Clavien-Dindo classification (Clavien 2009; Dindo 2004): Grade III or more.
   b. International Conference on Harmonisation - Good Clinical Practice guideline (ICH-GCP; ICH-GCP 1996): serious adverse events defined as any untoward medical occurrence that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, and results in persistent or significant disability/incapacity.
   c. Individual complications that could clearly be classified as Grade III or more with the Clavien-Dindo classification (Clavien 2009; Dindo 2004), or as a serious adverse event with the ICH-GCP classification.
3. Health-related quality of life (using any validated scale)
   a. Short-term (four weeks to three months)
   b. Medium-term (more than three months to one year)

Secondary outcomes

1. Recurrence (local recurrence, surgical wound recurrence (also called port site metastases in the laparoscopic group) or distal metastases)
   a. Short-term recurrence (within six months)
   b. Long-term recurrence (at maximal follow-up)
2. Adverse events (within three months). We accepted all adverse events reported by the study author irrespective of the severity of the adverse event.
3. Perioperative blood transfusion requirements (during surgery or within one week after surgery) (whole blood or red cell transfusion).
   a. Proportion of people requiring blood transfusion
   b. Quantity of blood transfusion
4. Measures of earlier postoperative recovery
   a. Length of hospital stay (including the index admission for gastrectomy and any surgical complication-related re-admission)
   b. Time to return to normal activity (return to preoperative mobility without any additional carer support)
   c. Time to return to work (in people who were employed previously)
5. Positive resection margins (presence of macroscopic or microscopic cancer tissue at the plane of resection) at histopathological examination after surgery.
6. Number of lymph nodes harvested during surgery.

We based the choice of the above clinical outcomes on the necessity to assess whether laparoscopic surgery results in adequate cancer clearance, is safe, and is beneficial in terms of decreased blood transfusion requirements; earlier postoperative recovery allowing earlier discharge from hospital, return to normal activity, and return to work; and improvement in health-related quality of life. We highlight that the positive resection margins at histopathological examination after surgery, and the number of harvested lymph nodes during surgery, are surrogate outcomes, and we have included these in order to explore whether these are responsible for any differences in survival or mortality.

We included studies which met the inclusion criteria, irrespective of whether they reported the secondary outcomes.

Search methods for identification of studies

Electronic searches

We conducted a literature search to identify all published and unpublished RCTs. The literature search identified potential studies in all languages. We translated the non-English language papers and assessed them fully for potential inclusion in the review as necessary.

We searched the following electronic databases for identifying potential studies.

1. The Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 9) (Appendix 1).

2. MEDLINE (1966 to September 2015) (Appendix 2).
3. EMBASE (1988 to September 2015) (Appendix 3).
4. Science Citation Index (1982 to September 2015) (Appendix 4).

We also conducted a search of ClinicalTrials.gov (ClinicalTrials.gov; Appendix 5) and the World Health Organization - International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en/; Appendix 6). We performed all the searches on 5 September 2015.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We contacted authors of identified trials and asked them to identify other published and unpublished studies.

We searched for errata or retractions from eligible trials on PubMed on 7 October 2015 (www.ncbi.nlm.nih.gov/pubmed).

Data collection and analysis

Selection of studies

Two review authors (LB and KG) independently screened titles and abstracts for inclusion all the potential studies that we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve' (ineligible). We retrieved the full text study reports for coded as 'retrieve' and two review authors (LB and KG) independently screened the full text, identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and Characteristics of excluded studies table.

Data extraction and management

We used a standard data collection form for study characteristics and outcome data that had been piloted on at least one study in the review. Two review authors (LB and KG) extracted study characteristics from included studies and detailed them in a Characteristics of included studies table. We extracted the following study characteristics.

1. Methods: study design, total duration of the study and run in, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: number, mean age, gender, tumour stage, tumour location, American Society of Anesthesiologists (ASA) status (ASA 2014), inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, and concomitant interventions.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (LB and KG) independently extracted outcome data from included studies. If outcomes were reported multiple times for the same time frame (for example, short-term health-related quality of life was reported at six weeks and three months), we chose the later time point (i.e. three months) for data extraction. For time-to-event outcomes where data is censored, we extracted data to calculate the natural logarithm of the hazard ratio (HR) and its standard error using the methods suggested in Parmar 1998.

We included all randomised participants for medium-term and long-term outcomes (e.g. mortality or quality of life), and this was not conditional upon the short-term outcomes (e.g. being alive at three months or having a low or high quality of life index at three months).

We noted in the Characteristics of included studies table if outcome data are reported in an unusable way. We resolved disagreements by consensus. One review author (LB) copied across the data from the data collection form into Review Manager 5 (RevMan 2014). We double-checked that the data were entered correctly by comparing the study reports with how the data are presented in the systematic review.

Assessment of risk of bias in included studies

Two review authors (LB and KG) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion. We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low, or unclear risk of bias and provided a quotation from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different from a participant-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trial author, we noted this in the 'Risk of bias' table.

We considered trials were at low risk of bias in all domains to be at overall low risk of bias. Other trials were considered to be at unclear or high risk of bias. When considering treatment effects, we took into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and reported any deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as risk ratios (RRs) with 95% CIs and continuous data as mean differences (MDs) with 95% CIs when the

outcome was reported or converted to the same units in all the trials (e.g. hospital stay, time to return to work) or standardised mean differences (SMDs) with 95% CIs when different scales were used for measuring the outcome (e.g. quality of life). We ensured that higher scores for continuous outcomes had the same meaning for the particular outcome, explained the direction to the reader, and reported where the directions were reversed, if this was necessary. We calculated the rate ratio (RaR) with 95% CIs for outcomes such as adverse events and serious adverse events, where it is possible for the same person to develop more than one adverse event (or serious adverse event). We did not identify any studies that reported the RaR of adverse events (or serious adverse events) in the intervention versus control based on Poisson regression. We calculated the HR for time-to-event outcomes such as long-term mortality, long-term recurrence, and time-to-first adverse event (or serious adverse event).

We undertook meta-analyses only where this was meaningful (i.e. if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense).

A common way that trial authors indicate when they have skewed data is by reporting medians and interquartile ranges. When we encountered this, we noted that the data were skewed by following the rough guide for identifying skewed distribution available in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and considered the implication of this.

Where multiple trial arms were reported in a single trial, we included only the relevant arms. If two comparisons (e.g. laparoscopy-assisted gastrectomy versus open gastrectomy and totally laparoscopic gastrectomy versus open gastrectomy) had to be entered into the same meta-analysis, we halved the control group to avoid double-counting. The alternative way of including such trials with multiple arms is to pool the results of the laparoscopy-assisted gastrectomy and totally laparoscopic gastrectomy and compare it with open gastrectomy. We performed a sensitivity analysis to determine if the results of the two methods of dealing with multi-arm trials led to different conclusions.

Unit of analysis issues

The unit of analysis was individual participants undergoing gastrectomy. We did not encounter any cluster-randomised trials for this review, and therefore did not require any specific methodology for this trial type.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). If we were unable to obtain the information from the investigators or study sponsors, we imputed mean from median (i.e. consider median as the mean) and standard deviation from standard error, interquartile range, or P values according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), but assessed the impact of including such studies in a sensitivity analysis. If we were unable to calculate the standard deviation from the standard error, interquartile range, or P values, we imputed the standard deviation as the highest standard deviation in the remaining trials included in the outcome, fully aware that this method of imputation will decrease the weight of the studies in the meta-analysis of MD and shift the effect towards no effect for SMD.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity as per the *Cochrane Handbook for Systematic Reviews of Interventions* (i.e. greater than 50% to 60%; Higgins 2011), we explored it by pre-specified subgroup analysis.

Assessment of reporting biases

We attempted to contact study authors, asking them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results using a sensitivity analysis**.**

If we were able to pool more than 10 trials, we created and examined a funnel plot to explore possible publication biases. We used Egger's test to determine the statistical significance of the reporting bias (Egger 1997). We considered a P value less than 0.05 statistically significant for reporting bias.

Data synthesis

We performed analyses using Review Manager 5 (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. Totally laparoscopic and laparoscopy-assisted gastrectomy.
2. Different cancer stages (early gastric cancer and advanced gastric cancer; node-positive and node-negative gastric cancer). For this, we defined early gastric cancer as tumours confined to mucosa and submucosa, irrespective of lymph node metastasis (Japanese Gastric Cancer Association 2011).
3. Different types of gastrectomy (proximal, pylorus-preserving, subtotal, total gastrectomy).
4. Different methods of anastomoses (stapler versus hand-sewn anastomoses).
5. People with different anaesthetic risk (ASA I (a healthy person) or ASA II (a person with mild systemic disease) versus ASA III or more (a person with severe systemic disease or worse).
6. Different body mass index (BMI) (healthy weight (BMI 18.5 to 25) versus overweight or obese (BMI 25 or greater).

We used all primary outcomes in subgroup analyses.

We used the formal Chi^2 test for subgroup differences to test for subgroup interactions.

Sensitivity analysis

We performed sensitivity analyses defined a priori, to assess the robustness of our conclusions. These involved:

1. excluding trials at unclear or high risk of bias (one of more of the risk of bias domains (other than blinding of surgeon) classified as unclear or high);
2. excluding trials in which either mean or standard deviation, or both are imputed;
3. excluding cluster-RCTs in which the adjusted effect estimates are not reported; and

4. different methods of dealing with multi-arm trials (see Measures of treatment effect).

'Summary of findings' table

We created two 'Summary of findings' tables. Summary of findings for the main comparison includes all of the pre-specified primary outcomes that have been reported in the studies (short-term mortality, long-term mortality, and serious adverse events); Summary of findings 2 includes all of the pre-specified secondary outcomes that have been reported in the studies (long-term recurrence, adverse events, perioperative blood transfused, length of hospital stay, and number of lymph nodes harvested). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it related to the studies that contributed data to the meta-analyses for the pre-specified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and using GRADEproGDT software (GRADEproGDT 2015). We justified all decisions to downgrade or upgrade the quality of studies using footnotes and made comments to aid reader's understanding of the review, where necessary. We considered whether there was any additional outcome information that we were unable to incorporate into the meta-analyses, noted this in the comments, and stated if it supported or contradicted the information from the meta-analyses.

Reaching conclusions

We based our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We avoided making recommendations for practice, and our Implications for research will give the reader a clear sense of where the focus of any future research in the area should be, and what the remaining uncertainties are.

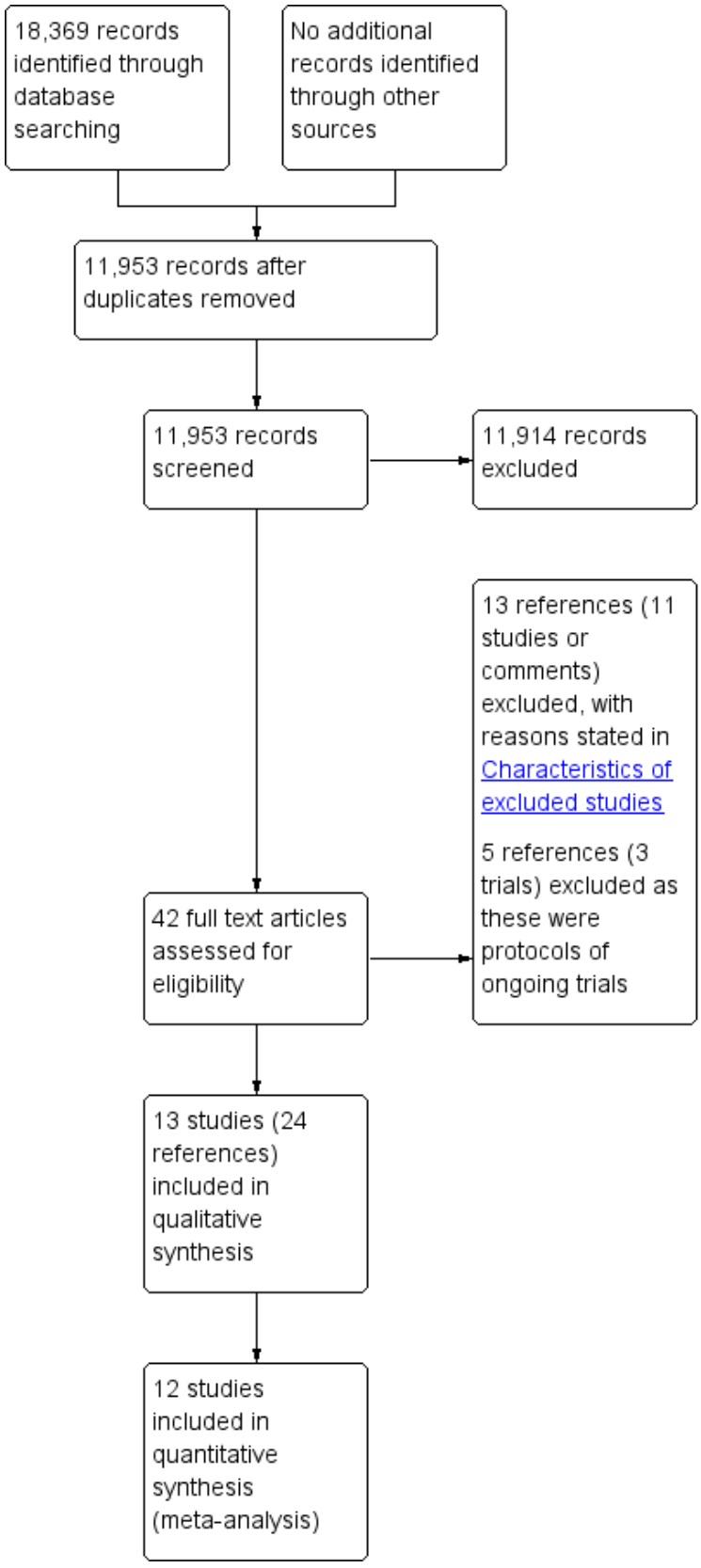
RESULTS

Description of studies

Results of the search

We identified 18,369 references through electronic searches of the Cochrane Central Register of Controled trials (CENTRAL), MEDLINE, EMBASE, Science Citation Index, ClinicalTrials.gov and WHO ICTRP (World Health Organization International Clinical Trials Registry Platform). After completion of manually removing duplicate references there were 11,953 references. We excluded 11,914 clearly irrelevant references through reading the abstracts. We sought 42 references in full text for further assessment. We did not identify any additional references to trials by searching the trial registry. We excluded 13 references (11 studies or comments) because of the reasons mentioned in the Characteristics of excluded studies tables and Excluded studies. We excluded five references (three trials) which were protocols of ongoing trials with no interim results available. Thirteen trials (24 references) met the inclusion criteria and were included in this review (Aoyama 2014; Cai 2011; Chen Hu 2012; Deng 2009; Hayashi 2005; Hu 2015; Huscher 2005; Kim 2013; Kim 2015; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013). The reference flow diagram is shown in Figure 3.

Figure 3. Study flow diagram.



Included studies

The thirteen trials compared laparoscopic with open gastrectomy (Aoyama 2014; Cai 2011; Chen Hu 2012; Deng 2009; Hayashi 2005; Hu 2015; Huscher 2005; Kim 2013; Kim 2015; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013). Twelve of the trials were two-armed RCTs (Aoyama 2014; Cai 2011; Deng 2009; Hayashi 2005; Hu 2015; Huscher 2005; Kim 2013; Kim 2015; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013). The thirteenth was a four-armed trial (Chen Hu 2012). Two of the arms involved laparoscopic surgery (fast-track laparoscopic gastrectomy versus standard procedure laparoscopic gastrectomy) and two arms involved open gastrectomy (fast-track laparoscopic gastrectomy versus standard procedure laparoscopic gastrectomy). The exact tumour stages included for each trial are reported in the Characteristics of included studies tables. Broadly, five trials included patients with early stage gastric cancer (Hayashi 2005; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013), three trials included patients with only advanced gastric cancer (Cai 2011; Kim 2013; Hu 2015), four trials included patients with early or advanced gastric cancer, a wide range of cancer staging (Aoyama 2014; Chen Hu 2012; Huscher 2005; Kim 2015), and one trial did not specify the cancer staging of included patients (Deng 2009).

Four of the trials included patients with an ASA risk score of III (Cai 2011; Hu 2015; Huscher 2005; Kim 2015), one trial did not include patients with ASA risk score III (Sakuramoto 2013), and the remaining eight trials did not specify their inclusion or exclusion (Aoyama 2014; Chen Hu 2012; Deng 2009; Hayashi 2005; Kim 2013; Kitano 2002; Lee 2005; Takiguchi 2013). None of the 13 trials specifically stated the inclusion or exclusion of patients with a BMI greater than 30.

Ten of the studies used laparoscopy-assisted gastrectomy (Aoyama 2014; Cai 2011; Chen Hu 2012; Hayashi 2005; Kim 2013; Kim 2015; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013), with three potentially using the totally laparoscopic method (Deng 2009; Hu 2015; Huscher 2005). There was no mention of an incision to remove the specimen in these trials, and the procedure was termed laparoscopic gastrectomy in these trials. However, it should be noted that some trials which were really laparoscopic-assisted gastrectomy (based on the description of the procedure) reported the procedure as laparoscopic gastrectomy. So, it is not clear whether any of the trials used totally laparoscopic gastrectomy.

Twelve of the trials involved patients in whom subtotal (distal) gastrectomy was performed (Aoyama 2014; Chen Hu 2012; Deng 2009; Hayashi 2005; Hu 2015; Huscher 2005; Kim 2013; Kim 2015; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013); in Cai 2011, proximal, distal or total gastrectomy was performed. D1 nodal dissection was performed in both groups in one trial (Hayashi 2005). D2 nodal dissection was performed in both groups in four trials (Cai 2011; Deng 2009; Hu 2015; Kim 2013). D1 or more nodal dissections were performed in both groups in three trials (Aoyama 2014; Huscher 2005; Kim 2015). In two trials, selected groups of lymph nodes were dissected in both groups (Sakuramoto 2013; Takiguchi 2013). In one trial, selected nodes were dissected in the laparoscopic group, while D2 nodal dissection was performed in the open group (Lee 2005). Information on nodal dissection was not available in two trials (Chen Hu 2012; Kitano 2002). Seven of the trials used the Billroth I method of anastomosis alone (Aoyama 2014; Deng 2009; Hayashi 2005; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013), four of the trials used either the Billroth I or II anastomosis, Roux en Y anastomosis, oesophagogastrostomy or oesophageal jejunostomy (Cai 2011; Chen Hu 2012; Huscher 2005; Kim 2015), and two did not state the method of anastomosis used (Hu 2015; Kim 2013). Five trials used staples as the anastomotic method (Aoyama 2014; Hayashi 2005; Lee 2005; Sakuramoto 2013; Takiguchi 2013). In the remaining trials, either a combination of stapler and hand-sewn anastomosis were used (Huscher 2005), or the information on stapler versus hand-sewn anastomosis was not available (Cai 2011; Chen Hu 2012; Deng 2009; Hu 2015; Kim 2013; Kim 2015; Kitano 2002). Drains were routinely used in both groups in one trial (Sakuramoto 2013), and no routine drains were used in either group in one trial (Aoyama 2014). In one 2 x 2 factorial trial in which the safety and effectiveness of laparoscopic versus open gastrectomy and fast-track surgery versus conventional surgery, drains were used in participants who underwent fast-track surgery in both the laparoscopic and open groups (Chen Hu 2012). Two trials reported drains being used in the laparoscopic gastrectomy group, but did not report whether drains were used routinely in the open gastrectomy group (Lee 2005; Takiguchi 2013). The information on drain use was not available in the remaining trials (Cai 2011; Deng 2009; Hayashi 2005; Hu 2015; Huscher 2005; Kim 2013; Kim 2015; Kitano 2002).

The follow-up period was not available for one trial (Hu 2015). The follow-up period in the remaining trials were as follows.

- Until discharge (Deng 2009; Sakuramoto 2013)
- 30 days (Aoyama 2014; Chen Hu 2012; Kim 2013; Kim 2015).
- 14 months (Lee 2005); 22 months (Cai 2011); 26 months (Kitano 2002).
- 42 months (Hayashi 2005); 52 months (Huscher 2005); 60 months (Takiguchi 2013).

In total, 2794 participants were randomised in the 13 trials included in this review. One trial which included 53 participants did not contribute any data for this review, because none of the outcomes included in the review were reported (Deng 2009). Two hundred and thirteen participants were excluded in the remaining 12 trials that contributed data, leaving a total of 2528 participants for whom data were available. Of these 2528 participants, 1288 were randomised to laparoscopic gastrectomy and 1240 to open gastrectomy (Aoyama 2014; Cai 2011; Chen Hu 2012; Hayashi 2005; Hu 2015; Huscher 2005; Kim 2013; Kim 2015; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013).

Excluded studies

We excluded a total of 13 references (11 studies or comments). We excluded three references because they were reports of a 'quasi-randomised' control trial in which block allocation equivalent to alternate assignment was used (Kim 2008). We excluded two references because they were comments on Kim 2008 (Kim 2009; Liakakos 2009), and we excluded one reference because it was an editorial (Kanellos 2009). We excluded seven references because they were not RCTs (Han 2014; Kawamura 2008; Lee 2008; Lee 2009; Li 2014; Lin 2014; Sakuramoto 2009).

We excluded five other references because they were protocols for three trials which have not yet reported the results (Haverkamp 2015; Straatman 2015; Yoshikawa 2012). A summary of these trials is reported in Characteristics of ongoing studies.

Risk of bias in included studies

All the trials were at unclear or high risk of bias as shown in Figure 1 and Figure 2.

Allocation

Four trials were free from selection bias (Aoyama 2014; Kim 2013; Kim 2015; Sakuramoto 2013). These trials had a low risk of bias in random sequence generation and allocation concealment. The remaining trials had unclear risk of bias in at least one of the aspects of random sequence generation or allocation concealment.

Blinding

Seven of the trials were at unclear risk of performance bias because of a lack of reported information (Aoyama 2014; Cai 2011; Deng 2009; Huscher 2005; Kim 2015; Kitano 2002; Lee 2005), with the remaining six being at high risk of performance bias, with patients and healthcare providers not being blinded (Chen Hu 2012; Hayashi 2005; Hu 2015; Kim 2013; Sakuramoto 2013; Takiguchi 2013).

Ten of the trials were at unclear risk of detection bias because of a lack of reported information (Aoyama 2014; Cai 2011; Chen Hu 2012; Deng 2009; Hayashi 2005; Huscher 2005; Kim 2013; Kim 2015; Kitano 2002; Lee 2005), with the remaining three being at high risk of detection bias, with outcome assessors not being blinded (Hu 2015; Sakuramoto 2013; Takiguchi 2013).

Incomplete outcome data

We classified three trials at low risk of attrition bias as they described no post-randomisation drop-outs (Hayashi 2005; Hu 2015; Takiguchi 2013). Four trials were at unclear risk of attrition bias as the reports did not describe the participant flow clearly (Aoyama 2014; Deng 2009; Kitano 2002; Lee 2005). Six trials were at high risk of attrition bias as they had post-randomisation drop-outs which were likely to affect the effect estimates (Cai 2011; Chen Hu 2012; Huscher 2005; Kim 2013; Kim 2015; Sakuramoto 2013).

Selective reporting

We classified six of the trials at low risk of reporting bias, with both postoperative mortality and morbidity reported (Aoyama 2014; Cai 2011; Chen Hu 2012; Hayashi 2005; Huscher 2005; Sakuramoto 2013). We classified seven of the trials at high risk of reporting bias, as one or both of these were not reported (Deng 2009; Hu 2015; Kim 2013; Kim 2015; Kitano 2002; Lee 2005; Takiguchi 2013).

Other potential sources of bias

In one trial, a more extensive procedure (subtotal gastrectomy) was performed in open gastrectomy group compared to laparoscopic group (distal gastrectomy) (Lee 2005). This could potentially favour the laparoscopic group in terms of decreased complications, but favour the open group in terms of decreased long-term recurrence and mortality. We did not detect any other sources of bias in the remaining trials.

Effects of interventions

See: **Summary of findings for the main comparison** Laparoscopic gastrectomy compared to open gastrectomy for gastric cancer (primary outcomes); **Summary of findings 2** Laparoscopic gastrectomy compared to open gastrectomy for gastric cancer (secondary outcomes)

The outcomes reported in these trials were: short-term mortality, long-term mortality, serious adverse events within three months, short-term recurrence, long-term recurrence, adverse events within three months, blood transfusion during or within a week of surgery, quantity of perioperative blood transfused, length of hospital stay, positive resection margins on histopathology, and number of lymph nodes harvested. The remaining outcomes of interest in the review, i.e. short- and medium-term health-related quality of life, time to return to normal activity, and time to return to work were not reported in any of the trials. The results are partially summarised in Summary of findings for the main comparison and Summary of findings 2.

Short-term mortality

Eleven trials reported short-term mortality which is defined as mortality in hospital or within thirty days of treatment (Aoyama 2014; Cai 2011; Chen Hu 2012; Hayashi 2005; Hu 2015; Huscher 2005; Kim 2015; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013). We pooled the trials using a fixed-effect model. There was no significant difference in the proportion of participants who died within 30 days of treatment between laparoscopic gastrectomy (7/1188: adjusted proportion (based on meta-analysis) = 0.6%) and open gastrectomy (4/1447: 0.3%) (RR 1.60, 95% CI 0.50 to 5.10; participants = 2335; studies = 11; I^2 = 0%; low quality evidence) (Analysis 1.1; Summary of findings for the main comparison). There was no change to the conclusions when we used a random-effects model or when we calculated the risk difference (RD 0.00, 95% CI -0.01 to 0.01; participants = 2335; studies = 11; I^2 = 0%).

Long-term mortality

Three trials reported long-term mortality (Cai 2011; Huscher 2005; Takiguchi 2013). In one of these trials, all the participants were alive after a follow-up period of 60 months (Takiguchi 2013). We pooled the trials using a fixed-effect model. There was no significant difference in long-term mortality between the groups (HR 0.94, 95% CI 0.70 to 1.25; participants = 195; studies = 3; I^2 = 0%; very low quality evidence) (Analysis 1.2; Summary of findings for the main comparison). There was no change to the conclusions when we used a random-effects model. Approximately 55% to 60% of participants were alive after about 52 months (Huscher 2005).

Serious adverse events within three months

Eight trials reported serious adverse events within three months of treatment (Aoyama 2014; Cai 2011; Chen Hu 2012; Hayashi 2005; Huscher 2005; Kitano 2002; Lee 2005; Sakuramoto 2013). The serious adverse events in the trials included anastomotic leakage, anastomotic stenosis requiring balloon dilatation, pancreatic fistula, pancreatic injury, small bowel volvulus requiring adhesiolysis, bleeding requiring reoperation, abdominal abscess, myocardial infarction, acute respiratory distress syndrome, pleural effusion requiring puncture, and pneumonia. The type of serious adverse events were similar in nature between the groups. We pooled the trials using a fixed-effect model. There was no significant difference in the proportion of participants who suffered a serious adverse event between laparoscopic gastrectomy (7/216: adjusted proportion = 3.6%) and open gastrectomy (13/216: 6%) within three months of treatment (RR 0.60, 95% CI 0.27 to 1.34; participants = 432; studies = 8; I^2 = 0%; very low quality evidence) (Analysis 1.3; Summary of findings for the main comparison). There

was no change to the conclusions when we used a random-effects model or when we calculated risk difference.

Health-related quality of life

Short- and medium-term health-related quality of life were not reported in any of the trials.

Short-term recurrence

Three trials reported short-term recurrence, which is defined as local recurrence, surgical wound recurrence or distal metastases within six months (Hayashi 2005; Kitano 2002; Lee 2005). No events were reported for either laparoscopic (52 participants) or open gastrectomy (51 participants). Therefore, we could not calculate an effect estimate (participants = 103; studies = 3) (Analysis 1.4).

Long-term recurrence

Four trials reported long-term recurrence (> six months) (Hayashi 2005; Huscher 2005; Kitano 2002; Lee 2005). Three of these three trials did not report any recurrence in either group (Hayashi 2005; Kitano 2002; Lee 2005). There was no significant difference in the hazard ratio for recurrence more than six months after treatment between the two groups (HR 0.95, 95% CI 0.70 to 1.30; participants = 160; studies = 4; very low quality evidence) (Analysis 1.5; Summary of findings 2). Since only one trial contributed to the analysis, the issue of fixed-effect versus random-effects meta-analysis and assessment of heterogeneity did not arise.

Adverse events within three months

Eleven trials reported adverse events within three months of treatment (Aoyama 2014; Cai 2011; Chen Hu 2012; Hayashi 2005; Hu 2015; Huscher 2005; Kim 2013; Kim 2015; Kitano 2002; Lee 2005; Sakuramoto 2013). We pooled the trials using a random-effects model. There were significantly fewer adverse events following laparoscopic gastrectomy (204/268: adjusted proportion = 16.1%) versus open gastrectomy (253/1222: 20.7%) (RR 0.78, 95% CI 0.60 to 1.01; participants = 2490; studies = 11; I^2 = 38%; very low quality evidence) (Analysis 1.6: Summary of findings 2). However, on using the fixed-effect model, there was no statistically significant difference between the groups (RR 0.78, 95% CI 0.66 to 0.92; participants = 2490; studies = 11; I^2 = 38%). Two large trials had narrow confidence intervals and had results in opposite directions, and this may account for the differences between the fixed-effect and random-effects models. In addition, we performed a sensitivity analysis excluding Lee 2005, in which the laparoscopic group underwent a less invasive procedure than the open group. There was no change in the results by excluding this trial.

Blood transfusion during or within a week of surgery

Two trials reported the proportion of patients requiring blood transfusion during or within a week of surgery (Aoyama 2014; Takiguchi 2013). None of the participants in either group in either of the trials required a blood transfusion. Therefore, we could not estimate an effect estimate (participants = 66; studies = 2) (Analysis 1.7). Since both trials reported the mean and standard deviation, we did not perform any sensitivity analysis excluding studies in which standard deviation was imputed.

Quantity of perioperative blood transfused

Two trials reported quantity of perioperative blood transfused (Cai 2011; Lee 2005): Lee 2005 reported the number of units of blood transfused; and Cai 2011 reported the amount of blood transfused in SI units. We pooled the trials using a fixed-effect model. There was no significant difference in the amount of blood transfused between the laparoscopic and open gastrectomy groups (SMD 0.05, 95% CI -0.27 to 0.38; participants = 143; studies = 2; I^2 = 0%; very low quality evidence) (Analysis 1.8; Summary of findings 2). There was no change to the conclusions when we used a random-effects model.

Length of hospital stay

Eight trials reported length of hospital stay (Cai 2011; Chen Hu 2012; Hayashi 2005; Huscher 2005; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013). The length of hospital stay was significantly shorter in the laparoscopic group than the open group (MD -1.38 days, 95% CI -2.57 to -0.19; participants = 444; studies = 8; I^2 = 76%; very low quality evidence) using the random-effects model (Analysis 1.9; Summary of findings 2). There was substantial heterogeneity as noted by I^2 of 76% and Chi^2 test for heterogeneity P value of 0.0001. Using the fixed-effect model did not alter the results (MD -0.86 days, 95% CI -1.27 to -0.44; participants = 444; studies = 8; I^2 = 76%). In two trials, median hospital stay rather than mean hospital stay was reported (Chen Hu 2012; Takiguchi 2013). In Takiguchi 2013, the standard deviation was calculated from the P value, while in Chen Hu 2012, the standard deviation was imputed as the highest standard deviation from the remaining trials. Excluding these two trials, there was no statistically significant difference between the two groups (MD -1.82 days, 95% CI -3.72 to 0.07; participants = 319; studies = 6; I^2 = 83%) using the random-effects model, although there was still a statistically significant difference between the groups using the fixed-effect model (MD -0.68 days, 95% CI -1.31 to -0.06; participants = 319; studies = 6; I^2 = 83%). The exclusion of Lee 2005, in which the laparoscopic group underwent a less invasive procedure did not alter the results.

Time to return to normal activity

This outcome was not reported in any of the trials.

Time to return to work

This outcome was not reported in any of the trials.

Positive resection margins at histopathological examination

One trial reported the number of patients with positive resection margins at histopathological examination (Kitano 2002). No events were reported for either laparoscopic or open gastrectomy. Therefore, we could not calculate an effect estimate (participants = 28; study = 1) (Analysis 1.10).

Number of lymph nodes harvested

Nine trials reported the number of lymph nodes harvested (Aoyama 2014; Cai 2011; Chen Hu 2012; Hayashi 2005; Huscher 2005; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013). We analysed the trials using a fixed-effect model. There was no significant difference in the number of lymph nodes harvested between the two groups (MD -0.63, 95% CI -1.51 to 0.25; participants = 472; studies = 9; I^2 = 40%; very low quality evidence) (Analysis 1.11; Summary of findings 2). There was no change to the conclusions when we used a random-effects model. Since higher numbers of lymph nodes harvested is a better surgical marker, we switched the direction of the X-axis in Analysis 1.11, with trials to the left of the equivalence

line favouring open gastrectomy. The mean or standard deviation or both were calculated from other information such as median, standard error, or P value or imputed from the maximum standard deviation in the included studies in four trials (Aoyama 2014; Chen Hu 2012; Huscher 2005; Takiguchi 2013). Excluding these trials did not alter the conclusions (MD -0.62, 95% CI -1.55 to 0.31; participants = 262; studies = 5; I^2 = 70%).

Subgroup analysis

Of the planned subgroup analyses for the primary outcomes, only two were possible.

1. Different cancer stages (early gastric cancer and advanced gastric cancer). There was no short-term mortality or long-term mortality in laparoscopic or open gastrectomy groups in the early gastric cancer subgroup. So, we could not perform tests for subgroup differences (Analysis 2.1; Analysis 2.2). The test for subgroup differences was not statistically significant for subgroup analysis of serious adverse events, and there was a good overlap of confidence interval between the effect estimates of the different subgroups (Analysis 2.3).
2. Different types of gastrectomy (subtotal versus total gastrectomy). Of the 13 trials, 12 trials reported the use of subtotal gastrectomy (Aoyama 2014; Chen Hu 2012; Deng 2009; Hayashi 2005; Hu 2015; Huscher 2005; Kim 2013; Kim 2015; Kitano 2002; Lee 2005; Sakuramoto 2013; Takiguchi 2013). In Cai 2011, a mixture of different types of gastrectomies was performed. No separate data were available for the different types of gastrectomies. Excluding this trial did not alter the results (Analysis 2.4; Analysis 2.5; Analysis 2.6).

The remaining subgroup analyses were not possible for the following reasons.

1. Totally laparoscopic and laparoscopy-assisted gastrectomy: it was not clear whether any of the trials used totally laparoscopic gastrectomy.
2. Different cancer stages (node-positive and node-negative gastric cancer): none of the trials reported the results separately for different nodal status.
3. Different methods of anastomoses (stapler versus hand-sewn anastomoses): five trials used staples as the anastomotic method (Aoyama 2014; Hayashi 2005; Lee 2005; Sakuramoto 2013; Takiguchi 2013). In the remaining trials, either a combination of stapler and hand-sewn anastomosis were used (Huscher 2005), or the information on stapler versus hand-sewn anastomosis was not available (Cai 2011; Chen Hu 2012; Deng 2009; Hu 2015; Kim 2013; Kim 2015; Kitano 2002).
4. People with different anaesthetic risk (ASA I (a healthy person) or ASA II (a person with mild systemic disease) versus ASA III or more (a person with severe systemic disease or worse): none of the trials that included ASA III participants reported the results separately for ASA III participants.
5. Different BMI (healthy weight (BMI 18.5 to 25) versus overweight or obese (BMI 25 or greater)): none of the trials reported results separately for people with different BMI ranges.

Sensitivity analysis

The sensitivity analysis excluding trials in which either mean or standard deviation or both were imputed have been presented in the individual outcomes. Another sensitivity analysis excluding the trial in which the laparoscopic group underwent less invasive distal gastrectomy, and the open group underwent more invasive subtotal gastrectomy, did not alter the results. We performed the remaining sensitivity analyses for the following reasons.

1. All trials were at unclear or high risk of bias.
2. No cluster-RCTs were included.
3. The only multi-armed trial included was investigating fast-track surgery. Since this variable was not of interest to this review, we considered the trial a two-arm trial.

Reporting bias

Only two outcomes had 10 or more trials, namely, short-term mortality and adverse events. We did not assess reporting bias using a funnel plot in the remaining comparisons. In the outcome, short-term mortality, only three trials had one or more events in at least one of the groups (Hu 2015; Huscher 2005; Kim 2015). So, we did not assess reporting bias using a funnel plot for short-term mortality either. Visual inspection revealed that studies with large variance were more prevalent in the laparoscopic group than the open group, suggesting potential reporting bias. However, the Egger's test was not statistically significant (P = 0.3144).

DISCUSSION

Summary of main results

In this review, we compared laparoscopic versus open gastrectomy for people with non-metastatic gastric cancer. There were no statistically significant differences in short-term mortality, long-term mortality, proportion of people with serious adverse events within three months of surgery, proportion of people with recurrence within six months, proportion of people with recurrence after six months, proportion of people requiring blood transfusion during or within a week of surgery, proportion of people with any adverse event within three months of surgery, quantity of perioperative blood transfused, proportion of people with positive resection margins at histopathological examination, or in the number of lymph nodes harvested by each technique. None of the trials reported patient oriented outcomes such as health-related quality of life, time to return to normal activity, or time to return to work.

Short-term mortality was reported in 2335 participants. Based on the number of participants included and the confidence intervals obtained by calculating the risk difference, it appears that there is no difference between laparoscopic and open gastrectomy in terms of mortality (i.e. this is lack of effect rather than lack of evidence of effect), although the risk of bias in the trials, mainly due to exclusion of participants who did not receive the planned treatment, introduces some doubt on this issue. Differences in serious adverse events within three months, length of hospital stay, long-term recurrence, and long-term mortality (which are the other major outcomes of interest for patients and healthcare funders) cannot be ruled out since the confidence intervals were wide.

Overall completeness and applicability of evidence

This review included participants undergoing either laparoscopic or open gastrectomy for gastric cancer. Although the American Society of Anesthesiologists (ASA) status was not reported in many trials, all the participants must have been fit for major surgery since both arms involve major surgeries. Thus, the results of this review

are applicable only to patients with gastric cancer, with a variety of stages from early to advanced cancer, and are not applicable to patients who are not suitable for surgery either because of their anaesthetic risk or because of the location or presence of metastatic disease. It should also be noted that the results apply only to laparoscopy-assisted distal gastrectomy since it was not clear whether three trials that did not report a small laparotomy incision performed totally laparoscopic gastrectomy, and because most trials in this review included participants undergoing distal gastrectomy.

Quality of the evidence

All the trials were at unclear or high risk of bias. Selection bias and funding bias were at unclear or low risk of bias in all trials. Those trials with unclear risk of bias were generally due to a lack of clear information. We graded both performance and detection bias as high risk of bias in a significant number of trials, with issues in blinding of the healthcare providers responsible for these. There was significant bias due to missing outcomes in the trials, with six of the studies at high risk of bias because of post-randomisation drop-outs. This can be easily avoided by using an intention-to-treat analysis, which involves reporting the outcomes for all randomised patients even if they do not receive the relevant treatment. There was significant selective reporting bias in the trials, with seven of the studies at high risk of bias generally because morbidity was not reported adequately. Severity of the outcomes is more important than stating whether an adverse event occurred.

There was significant heterogeneity in length of hospital stay. Because of the few trials included in each subgroup, the subgroup analysis may not be reliable and multiple subgroup analyses can lead to spurious results. A potential reason for this heterogeneity may be different criteria for discharging patients who had undergone gastrectomy in different trials. The trials did not report this sufficiently to determine if this was the reason for the differences in effect estimates in trials.

There was imprecision in many outcomes despite the inclusion of more than 2500 participants in the various trials included in this review. This was because of selective outcome reporting with trials not reporting even important outcomes such as serious adverse events.

Despite the shortcomings in the studies included in this review, these studies constitute the best level of evidence that is currently available. Overall, the evidence from this systematic review is more trustworthy than observational studies and expert opinions. This is because observational studies contain inherent bias. It is quite possible that people with lower tumour burden will be selected to undergo laparoscopic gastrectomy while those with greater tumour burden will undergo open gastrectomy. This will lead to bias due to confounding in observational studies.

Potential biases in the review process

We followed the *Cochrane Handbook for Systematic Reviews of Interventions* for this review (Higgins 2011). There were no language, publication status, or sample size restrictions. Thus, we minimised the bias due to selection of trials. There was suspicion of reporting bias for adverse events by visual inspection of funnel plots, although this was not substantiated by Egger's test. Since there was no restriction on the publication date, we included trials from the pre-mandatory trial registration era. There is a possibility that some of the trials were not reported because of the direction of results. However, we have to be pragmatic and accept that it will be difficult to obtain useful data from these trials after such a long period of time. So, we have to arrive at conclusions based on the trials which have been published or reported in conferences. We calculated the hazard ratio for long-term mortality and long-term recurrence using methods suggested in Parmar 1998. This assumes constant proportional hazards. From the Kaplan-Meier curves in the studies, the proportional hazards appeared constant for both long-term mortality and long-term recurrence.

Agreements and disagreements with other studies or reviews

This is the first Cochrane review to assess laparoscopic versus open gastrectomy for gastric cancer. We identified three previous systematic reviews of RCTs on this topic (Jiang 2013; Liang 2011; Sun 2012). The authors of these systematic reviews appear to suggest that laparoscopic surgery is better than open surgery for one or more short-term outcomes, in particular, length of hospital stay. However, we are more cautious in concluding that laparoscopic surgery is better than open surgery because of the risk of bias in the studies included and the heterogeneity in the length of hospital stay.

AUTHORS' CONCLUSIONS

Implications for practice

Based on low quality evidence, there is no difference in short-term mortality between laparoscopic and open gastrectomy. Based on very low quality evidence, there is no evidence for any differences in short-term or long-term outcomes between laparoscopic and open gastrectomy. However, the data are sparse and the confidence intervals were wide suggesting that significant benefits or harms of laparoscopic gastrectomy cannot be ruled out.

Implications for research

Several trials are currently being conducted and interim results of these trials have been included in this review. These trials need to perform intention-to-treat analysis to ensure that the results are reliable and report the results according to the CONSORT statement (CONSORT 2010). If new trials are designed, they need to be designed according to the SPIRIT statement (SPIRIT 2013).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aoyama 2014

Methods	Randomised controlled trial
Participants	Country: Japan Number randomised: 26 Post-randomisation drop-outs: not stated Number analysed: 26 Average age: 65 years Females: 12 (46.2%) Method of Anastamosis: Billroth-I; stapler Type of gastrectomy: Subtotal gastrectomy Cancer stage: Early or advanced stage ($T_{1-2}N_{0-1}$) Totally laparoscopic or LAG: LAG **Inclusion criteria** Patients undergoing distal gastrectomy for stage I gastric cancer
Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 13) Further details: 5 or 6 ports; incision ≤ 6 cm Group 2: open gastrectomy (n = 13) Further details: Upper midline incision (xiphoid to umbilicus) Nodes dissected and drain use: D1 or more nodal dissection; no routine drain
Outcomes	The outcomes reported were short-term mortality, complications, and lymph nodes harvested
Notes	Conversion to open gastrectomy: 0/13 (0%) Follow-up period: 30 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients are randomized to either the ODG arm or the LADG arm by minimization method balancing the arms with institution and clinical stage (IA/IB)" Comment: This information was not available
Allocation concealment (selection bias)	Low risk	Quote: "After the confirmation of the eligibility criteria, registration is made by telephone, fax or web-based system to the JCOG Data Center. Patients are randomized to either the ODG arm or the LADG arm by minimization method balancing the arms with institution and clinical stage (IA/IB)" Comment: This information was not available

Aoyama 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: This information was not available
Selective reporting (reporting bias)	Low risk	Comment: Postoperative mortality and morbidity were reported
Other bias	Low risk	Comment: No other source of bias was identified

Cai 2011

Methods	Randomised controlled trial
Participants	Country: China Number randomised: 123 Post-randomisation drop-outs: 27 (22%) Number analysed: 96 Average age: 60 years Females: 20 (20.8%) Method of Anastamosis: Billroth-I, Billroth-II, oesophagogastrostomy and oesophageal jejunostomy; hand-sewn or stapler anastomosis not stated Type of gastrectomy: Proximal, distal, or total gastrectomy Cancer stage: Advanced stage ($T_{2\text{-}3}N_{\text{not stated}}$) Totally laparoscopic or LAG: LAG **Inclusion criteria** Patients requiring gastrectomy for gastric cancer **Exclusion criteria** 1. Patients needed thoraco-abdominal surgery 2. Patients with other malignant tumours 3. Patients with upper abdominal large operation history who cannot be fitted for LAG 4. Patients with gastric stump cancer and recurrent cancer 5. Patients with a surgical risk greater than ASA grade III 6. Patients with operative cardiovascular risk greater than New York Heart Association grade II 7. Severe liver disease (Child B or C) and renal dysfunction
Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 49) Further details: 5 ports; upper midline incision about 6 cm Group 2: open gastrectomy (n = 47) Further details: Upper midline incision (20 cm) Nodes dissected and drain use: D2 nodal dissection; drain use not stated

Cai 2011 *(Continued)*

Outcomes	The outcomes reported were short-term mortality, complications, lymph nodes harvested, length of hospital stay, and long-term mortality
Notes	Conversion to open gastrectomy: 2/61 (3.3%) Follow-up period: 22 months Reasons for post-randomisation drop-outs: not clearly reported. The authors state that they performed a subgroup analysis of patients with advanced stage cancer only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Comment: Postoperative mortality and morbidity were reported
Other bias	Low risk	Comment: No other source of bias was identified

Chen Hu 2012

Methods	Randomised controlled trial
Participants	Country: China Number randomised: 88 Post-randomisation drop-outs: 5 (5.7%) Number analysed: 83 Average age: 63 years Females: 41 (49.4%) Method of Anastamosis: Billroth-I or Billroth-II; hand-sewn or stapler anastomosis not stated Type of gastrectomy: Subtotal gastrectomy Cancer stage: Early or advanced stage ($T_{1-4}N_{not\ stated}$) Totally laparoscopic or LAG: LAG **Inclusion criteria** 1. Age 25–75 years old 2. Male or female

Chen Hu 2012 *(Continued)*

	3. Diagnosis confirmed by endoscopic biopsy 4. No lymph node or distant metastasis diagnosed by preoperative abdominal computed tomography 5. No history of autoimmune or severe cardiopulmonary diseases 6. No preoperative radiotherapy or chemotherapy 7. No digestive obstruction, perioperative blood or albumin infusion, combined intraoperative eviscer-ation 8. Acceptance by the patients and their families
Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 41) Further details: number of ports not stated; upper midline incision (5 to 8 cm) Group 2: open gastrectomy (n = 44) Further details: Upper midline incision (xiphoid to umbilicus or 2 cm below umbilicus) Nodes dissected and drain use: Nodal dissection not stated; routine drains were used in the part of group who underwent fast-track surgery
Outcomes	The outcomes reported were short-term mortality, complications, lymph nodes harvested, and hospi-tal stay
Notes	Conversion to open gastrectomy: not reported Follow-up period: 30 days Reasons for post-randomisation drop-outs: withdrew consent (3); lost to follow-up 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera-tion (selection bias)	Unclear risk	Comment: This information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available
Blinding of participants and personnel (perfor-mance bias) All outcomes	High risk	Quote: "Blinding of the surgeons and nurses was not feasible. Therefore, two specially trained doctors blinded to patients' allocated treatment group were in charge for assessing postoperative outcomes and follow-up"
Blinding of outcome as-sessment (detection bias) All outcomes	Unclear risk	Quote: "Blinding of the surgeons and nurses was not feasible. Therefore, two specially trained doctors blinded to patients' allocated treatment group were in charge for assessing postoperative outcomes and follow-up" Comment: It was not clear whether outcomes such as decision to discharge were made by the blinded outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: There were post-randomisation drop-outs
Selective reporting (re-porting bias)	Low risk	Comment: Postoperative mortality and morbidity were reported
Other bias	Low risk	Comment: No other source of bias was identified

Deng 2009

Methods	Randomised controlled trial
Participants	Country: China Number randomised: 53 Post-randomisation drop-outs: not stated Number analysed: 53 Average age: 51 years Females: 27 (50.9%) Method of Anastamosis: Billroth-I; hand-sewn or stapler anastomosis not stated Type of gastrectomy: Subtotal gastrectomy Cancer stage: not stated ($T_{not\ stated}N_{not\ stated}$) Totally laparoscopic or LAG: Possibly totally laparoscopic **Inclusion criteria** Patients undergoing distal gastrectomy for gastric cancer **Exclusion criteria** 1. Preoperative chemotherapy 2. Severe metabolic disorders 3. Endocrine or immune system diseases
Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 26) Further details: 5 ports Group 2: open gastrectomy (n = 27) Further details: Upper midline incision Nodes dissected and drain use: D2 nodal dissection; drain use not stated
Outcomes	None of the outcomes of interest were reported
Notes	Conversion to open gastrectomy: not reported Follow-up period: until discharge

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available
Incomplete outcome data (attrition bias)	Unclear risk	Comment: This information was not available

Deng 2009 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Comment: Postoperative mortality and morbidity were not reported
Other bias	Low risk	Comment: No other source of bias was identified

Hayashi 2005

Methods	Randomised controlled trial
Participants	Country: Japan Number randomised: 28 Post-randomisation drop-outs: 0 (0%) Number analysed: 28 Average age: 59 years Females: 6 (21.4%) Method of Anastamosis: Billroth-I; stapler Type of gastrectomy: Subtotal gastrectomy Cancer stage: Early stage ($T_1N_{not\ stated}$) Totally laparoscopic or LAG: LAG **Inclusion criteria** Patients undergoing distal gastrectomy for early gastric cancer **Exclusion criteria** 1. Cancer suitable for EMR 2. Cancer located in the upper half of the stomach 3. Age exceeding 80 years 4. Operative cardiovascular risk greater than New York Heart Association II 5. Severe liver disease (Child B or C) and renal dysfunction 6. No consent to participate in the study
Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 14) Further details: 4 ports; upper transverse incision about 6 cm Group 2: open gastrectomy (n = 14) Further details: Upper midline incision Nodes dissected and drain use: D1 nodal dissection; drain use not stated
Outcomes	The outcomes reported were short-term mortality, complications, lymph nodes harvested, length of hospital stay, and long-term mortality
Notes	Conversion to open gastrectomy: 0/14 (0%) Follow-up period: 42 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available

Hayashi 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Randomization of the patients into two groups (LADG or ODG) was performed by the blind envelope method on the day before surgery, and the patients were informed of the results the same day"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Randomization of the patients into two groups (LADG or ODG) was performed by the blind envelope method on the day before surgery, and the patients were informed of the results the same day"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Comment: Postoperative mortality and morbidity were reported
Other bias	Low risk	Comment: No other source of bias was identified

Hu 2015

Methods	Randomised controlled trial
Participants	Country: China Number randomised: 607 Post-randomisation drop-outs: 0 (0%) Number analysed: 607 Average age: not stated Females: not stated Method of Anastamosis: no information on type of anastomosis; hand-sewn or stapler anastomosis not stated Type of gastrectomy: Subtotal gastrectomy Cancer stage: Advanced stage ($T_{2\text{-}4}N_{0\text{-}3}$) Totally laparoscopic or LAG: Possibly totally laparoscopic **Inclusion criteria** 1. Age from over 18 to under 75 years 2. Primary gastric adenocarcinoma (papillary, tubular, mucinous, signet ring cell, or poorly differentiated) confirmed pathologically by endoscopic biopsy 3. cT2-4a, N0-3, M0 at preoperative evaluation according to the AJCC Cancer Staging Manual Seventh Edition 4. Expected curative resection through distal subtotal gastrectomy with D2 lymphadenectomy 5. Performance status of 0 or 1 on ECOG (Eastern Cooperative Oncology Group) scale 6. ASA score class I, II, or III 7. Written informed consent **Exclusion criteria** 1. Women during pregnancy or breast-feeding 2. Severe mental disorder 3. History of previous upper abdominal surgery (except laparoscopic cholecystectomy)

Hu 2015 *(Continued)*

4. History of previous gastrectomy, endoscopic mucosal resection or endoscopic submucosal dissection
5. Enlarged or bulky regional lymph node diameter over 3 cm by preoperative imaging
6. History of other malignant disease within past five years
7. History of previous neoadjuvant chemotherapy or radiotherapy
8. History of unstable angina or myocardial infarction within past six months
9. History of cerebrovascular accident within past six months
10. History of continuous systematic administration of corticosteroids within one month
11. Requirement of simultaneous surgery for other disease
12. Emergency surgery due to complication (bleeding, obstruction or perforation) caused by gastric cancer
13. FEV1 < 50% of predicted values

Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 308) Further details: number of ports not stated Group 2: open gastrectomy (n = 299) Further details: Incision not stated Nodes dissected and drain use: D2 nodal dissection; drain use not stated
Outcomes	The outcomes reported were short-term mortality and complications
Notes	Conversion to open gastrectomy: 14/308 (4.5%) Follow-up period: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Masking: Open Label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Masking: Open Label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation drop-outs
Selective reporting (reporting bias)	High risk	Comment: The severity of postoperative complications was not reported
Other bias	Low risk	Comment: No other source of bias was identified

Huscher 2005

Methods	Randomised controlled trial
Participants	Country: Italy Number randomised: 70 Post-randomisation drop-outs: 11 (15.7%) Number analysed: 59 Average age: 64 years Females: 20 (33.9%) Method of Anastamosis: Billroth-I or Billroth-II; some anastomoses by stapler and others by hand-sewn anastomoses Type of gastrectomy: Subtotal gastrectomy Cancer stage: Early or advanced stage ($T_{1-4}N_{0-2}$) Totally laparoscopic or LAG: Possibly totally laparoscopic **Inclusion criteria** Patients undergoing subtotal gastrectomy for distal gastric cancer
Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 30) Further details: 4 ports Group 2: open gastrectomy (n = 29) Further details: Incision not stated Nodes dissected and drain use: D1 or D2 nodal dissection; drain use not stated
Outcomes	The outcomes reported were short-term mortality, complications, lymph nodes harvested, length of hospital stay, long-term mortality, and long-term recurrence
Notes	Conversion to open gastrectomy: not reported Follow-up period: 52 months Reasons for post-randomisation drop-outs: extension beyond distal cancer; metastases

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: There were post-randomisation drop-outs
Selective reporting (reporting bias)	Low risk	Comment: Postoperative mortality and morbidity were reported

Huscher 2005 *(Continued)*

Other bias	Low risk	Comment: No other source of bias was identified

Kim 2013

Methods	Randomised controlled trial
Participants	Country: South Korea Number randomised: 204 Post-randomisation drop-outs: 9 (4.4%) Number analysed: 195 Average age: not stated Females: not stated Method of Anastamosis: no information on type of anastomosis; hand-sewn or stapler anastomosis not stated Type of gastrectomy: Subtotal gastrectomy Cancer stage: Advanced stage ($T_{2-4}N_{0-3}$) Totally laparoscopic or LAG: LAG **Inclusion criteria** 1. Patients with clinically advanced stage non metastatic, histologically proven gastric cancer (cT2-4 N0-3 M0) according to the sixth union for international cancer control edition) 2. Aged between 20 to 80 years **Exclusion criteria** 1. Participation in another trial interfering with the outcome of this study 2. Language problems 3. Lack of compliance 4. Mental inability 5. Synchronous or previous malignant disease (except curatively treated in situ cervical cancer or curatively resected non-melanoma skin cancer) 6. Systemic administration of corticosteroids 7. Unstable angina or myocardial infarction within 6 months of the trial 8. Severe respiratory disease 9. ASA score $>$ 3 10. Previous major abdominal surgery 11. Previous chemo- or radiotherapy 12. Inadequate liver, kidney- and bone-marrow functions 13. Eastern Cooperative Oncology Group status $>$ 1
Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 100) Further details: number of ports and incision size not stated Group 2: open gastrectomy (n = 95) Further details: Incision not stated Nodes dissected and drain use: D2 nodal dissection; drain use not stated
Outcomes	The outcomes reported were complications
Notes	Conversion to open gastrectomy: not reported Follow-up period: 30 days

Kim 2013 *(Continued)*

	Reasons for post-randomisation drop-outs: protocol violation and withdrawal of patient permission

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization is performed as block randomization in fixed block sizes in a 1:1 allocation ratio using a centralized web-based randomization system (eVelos [http://eresearch.ncc. re.kr/eres/jsp/ereslogin.jsp])"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization is performed as block randomization in fixed block sizes in a 1:1 allocation ratio using a centralized web-based randomization system (eVelos [http://eresearch.ncc. re.kr/eres/jsp/ereslogin.jsp])"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Blinding procedures are not possible in this trial due to the nature of the intervention"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "However blinded assessment of the primary & secondary outcomes were provided by blinded observers" (author replies) Comment: It is unclear how the decision on hospital discharge and serious adverse events were assessed (for example, by a second surgical team)
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: There were post-randomisation drop-outs
Selective reporting (reporting bias)	High risk	Comment: Mortality and the severity of postoperative complications were not reported
Other bias	Low risk	Comment: No other source of bias was identified

Kim 2015

Methods	Randomised controlled trial
Participants	Country: South Korea Number randomised: 1416 Post-randomisation drop-outs: 160 (11.3%) Number analysed: 1256 Average age: not stated Females: not stated Method of Anastamosis: Billroth-I, Billroth-II, or Roux-en-Y anastomosis; hand-sewn or stapler anastomosis not stated Type of gastrectomy: Subtotal gastrectomy Cancer stage: Early or advanced stage ($T_{1-2}N_{0-1}$) Totally laparoscopic or LAG: LAG **Inclusion criteria** 1. Pathologically proven gastric adenocarcinoma 2. Age of 20 to 80 years 3. A preoperative stage of cT1N0M0, cT1N1m0, cT2aN0M0 according to American Joint Committee on Cancer/Union for International Cancer Control 6th edition

Kim 2015 *(Continued)*

4. No history of other cancers
5. No history of chemotherapy or radiotherapy

Exclusion criteria

1. ASA class > 3
2. Need for combined resection
3. Total gastrectomy

Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 644) Further details: number of ports and incision size not stated Group 2: open gastrectomy (n = 612) Further details: Incision not stated Nodes dissected and drain use: D1 or more nodal dissection; drain use not stated
Outcomes	The outcomes reported were short-term mortality and complications
Notes	Conversion to open gastrectomy: not reported Follow-up period: 30 days Reasons for post-randomisation drop-outs: Patients who switched to the other group's approach and underwent other than distal gastrectomy or combined resection except cholecystectomy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After confirming the patients met the inclusion/exclusion criteria by telephoning the data center, the patients were registered into the trial and then randomized to one of two groups (LADG or ODG) on the basis of a computer-generated randomization list"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was coordinated centrally by the independent data center and aimed to balance the arms according to each institution"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: There were post-randomisation drop-outs
Selective reporting (reporting bias)	High risk	Comment: The severity of postoperative complications was not reported
Other bias	Low risk	Comment: No other source of bias was identified

Kitano 2002

Methods	Randomised controlled trial
Participants	Country: Japan Number randomised: 28 Post-randomisation drop-outs: not stated Number analysed: 28 Average age: 62 years Females: 11 (39.3%) Method of Anastamosis: Billroth-I; hand-sewn or stapler anastomosis not stated Type of gastrectomy: Subtotal gastrectomy Cancer stage: Early stage (T_1N_0) Totally laparoscopic or LAG: LAG **Inclusion criteria** 1. Patients undergoing distal gastrectomy for early gastric cancer 2. At risk of perigastric lymph node metastasis precluding endoscopic mucosal resection **Exclusion criteria** 1. Age over 80 years 2. Operative cardiovascular risk greater than that of New York Heart Association class II 3. Operative pulmonary risk greater than that of Hugh-Jones class II 4. Severe liver disease (Child class B or C) or renal dysfunction
Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 14) Further details: number of ports not stated; upper midline incision (5 cm) Group 2: open gastrectomy (n = 14) Further details: Upper midline incision Nodes dissected and drain use: Nodal dissection not stated; drain use not stated
Outcomes	The outcomes reported were short-term mortality, complications, and long-term recurrence
Notes	Conversion to open gastrectomy: 0/14 (0%) Follow-up period: 26 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available
Allocation concealment (selection bias)	Low risk	Quote: "After providing written informed consent, the patients were randomly assigned to either LADG group (n = 10) and an ODG group (n = 10) with Billroth-I reconstruction on the day before operation by use of numbered, sealed envelopes that were stratified by the surgeon"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: This information was not available

Kitano 2002 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: This information was not available
Selective reporting (reporting bias)	High risk	Comment: The severity of postoperative complications was not reported
Other bias	Low risk	Comment: No other source of bias was identified

Lee 2005

Methods	Randomised controlled trial
Participants	Country: South Korea Number randomised: 47 Post-randomisation drop-outs: not stated Number analysed: 47 Average age: 58 years Females: 21 (44.7%) Method of Anastamosis: Billroth-I; stapler Type of gastrectomy: Subtotal gastrectomy Cancer stage: Early stage (T_1N_0) Totally laparoscopic or LAG: LAG **Inclusion criteria** Patients with early gastric cancer undergoing distal gastrectomy **Exclusion criteria** 1. Patients who had mucosal lesions that were suitable for an endoscopic mucosal resection (lesion size < 20 mm in the elevated type and < 10 mm in the depressed type) 2. A surgical risk greater than ASA III 3. Lesions proximal to the midbody 4. A previous history of upper abdominal surgery 5. Need for combined surgery to treat another disease
Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 24) Further details: 4 ports; upper midline incision about 7 cm Group 2: open gastrectomy (n = 23) Further details: Upper midline incision (about 20 cm) Nodes dissected and drain use: Selected nodes in laparoscopic group and D2 nodal dissection in open group; drain used routinely in laparoscopic group; information on drain use in open group was not available
Outcomes	The outcomes reported were short-term mortality, complications, lymph nodes harvested, length of hospital stay, and long-term recurrence
Notes	Conversion to open gastrectomy: 0/24 (0%) Follow-up period: 14 months

Lee 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a random number table, 23 patients were assigned to the open surgery group (group O) and 24 patients were assigned to the LADG group (group L)"
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: This information was not available.
Selective reporting (reporting bias)	High risk	Comment: The severity of postoperative complications was not reported
Other bias	High risk	Comment: A more extensive procedure was performed in open gastrectomy group compared to laparoscopic group. This could potentially favour laparoscopic group in terms of decreased complications but favour open group in terms of decreased long-term recurrence and mortality

Sakuramoto 2013

Methods	Randomised controlled trial
Participants	Country: Japan Number randomised: 64 Post-randomisation drop-outs: 1 (1.6%) Number analysed: 63 Average age: 60 years Females: 21 (33.3%) Method of Anastamosis: Billroth-I; stapler Type of gastrectomy: Subtotal gastrectomy Cancer stage: Early stage (T_1N_0) Totally laparoscopic or LAG: LAG **Inclusion criteria** Over 20 and under 75 years of age with gastric cancer in the middle or lower part of the stomach for which distal gastrectomy was indicated **Exclusion criteria** 1. Past history of gastric cancer 2. Previous open surgery of the upper abdomen

Sakuramoto 2013 *(Continued)*

	3. Past history of other types of cancers and cancer treatment 4. Serious heart, lung, kidney, blood and/or metabolic disease 5. New York Heart Association class III or IV classification of cardiac patients 6. Class III, IV, or V of the Hugh-Jones dyspnoea criteria
Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 31) Further details: 4 ports; upper abdominal incision about 5 cm Group 2: open gastrectomy (n = 32) Further details: Upper midline incision (xiphoid to umbilicus) Nodes dissected and drain use: Selected group of nodes in the two groups; drains used routinely in both groups
Outcomes	The outcomes reported were short-term mortality, complications, and length of hospital stay
Notes	Conversion to open gastrectomy: not reported Follow-up period: until discharge Reasons for post-randomisation drop-outs: concurrent illness

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The computer-generated, nonstratified, blocked randomization scheme was managed centrally and concealed at the moment of inclusion"
Allocation concealment (selection bias)	Low risk	Quote: "The computer-generated, nonstratified, blocked randomization scheme was managed centrally and concealed at the moment of inclusion"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Due to the pragmatic nature of the trial, surgeons, care providers, and patients could not be blinded to the type of treatment that was performed".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Due to the pragmatic nature of the trial, surgeons, care providers, and patients could not be blinded to the type of treatment that was performed"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: There were post-randomisation drop-outs
Selective reporting (reporting bias)	High risk	Comment: Postoperative mortality and morbidity were reported
Other bias	Low risk	Comment: No other source of bias was identified

Takiguchi 2013

Methods	Randomised controlled trial
Participants	Country: Japan Number randomised: 40 Post-randomisation drop-outs: not stated

Takiguchi 2013 *(Continued)*

	Number analysed: 40 Average age: 62 years Females: 15 (37.5%) Method of Anastamosis: Billroth-I; stapler Type of gastrectomy: Subtotal gastrectomy Cancer stage: Early stage (T_1N_{0-1}) Totally laparoscopic or LAG: LAG **Inclusion criteria** 1. Age between 20 and 80 years 2. Performance status of ECOG (Eastern Cooperative Oncology Group) 0–1 3. Signed informed consent 4. Location of the primary tumour in the antrum, angle, and lower body 5. Histologically confirmed adenocarcinoma of the stomach with preoperative staging of stage Ia or Ib (no evidence of distant metastasis or invasion of adjacent organs or serosal infiltration by abdominal computed tomography [CT] and chest x-ray film and regional lymph node metastasis confined to perigastric nodes [n1] as shown on CT scan) **Exclusion criteria** 1. Metastatic disease 2. Previous history of malignancy in any organ 3. Any comorbidity obviating major surgery 4. Contraindication to laparoscopy such as severe cardiac disease, abdominal wall hernias, portal hypertension, pregnancy, previous upper abdominal major surgery excluding appendectomy and laparoscopic cholecystectomy. 5. Complicated cases requiring emergency surgery 6. An accompanying surgical condition requiring surgery at the same time
Interventions	Participants were randomly assigned to two groups Group 1: laparoscopic gastrectomy (n = 20) Further details: 5 ports; midline incision about 4 to 6 cm Group 2: open gastrectomy (n = 20) Further details: Incision not stated Nodes dissected and drain use: Selected group of nodes in the two groups; drains used in laparoscopic group, no details in open group
Outcomes	The outcomes reported were short-term mortality, blood transfusion, length of hospital stay, lymph node harvest, and long-term mortality
Notes	Conversion to open gastrectomy: 0/20 (0%) Follow-up period: 60 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available
Allocation concealment (selection bias)	Low risk	Quote: "Randomization of the patients into two groups was performed by the blind envelop method on the day before operation, but the patients were not informed of the results at that time"

Takiguchi 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was a single-blinded study in which only patients were blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: This was a single-blinded study in which only patients were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation drop-outs
Selective reporting (reporting bias)	High risk	Comment: The complications in the laparoscopic gastrectomy group and the severity of postoperative complications in the open gastrectomy group were not reported
Other bias	Low risk	Comment: No other source of bias was identified

ASA: American Society of Anesthesiologist; **EMR**: Endoscopic mucosal resection; **FEV1**: forced expiratory volume in first second; **JCOG**: Japan Clinical Oncology Group; **LADG**: laparoscopy-assisted distal gastrectomy; **LAG**: laparoscopy-assisted gastrectomy; **ODG**: open distal gastrectomy
T: Tumour stage of TNM classification
N: Nodal stage of TNM classification
Example: $T_{1\text{-}2}N_{0\text{-}1}$: indicates T-stage 1 or 2 and N-stage 0 or 1
Early gastric cancer: clinical stage: T_1N_{any}
Advaced gastric cancer: $T_{>1}N_{any}$

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Han 2014	Not a randomised controlled trial
Kanellos 2009	Editorial
Kawamura 2008	Not a randomised controlled trial
Kim 2008	Quasi-randomised study
Kim 2009	Comment on an excluded study (Kim 2008)
Lee 2008	Not a randomised controlled trial
Lee 2009	Not a randomised controlled trial
Li 2014	Not a randomised controlled trial
Liakakos 2009	Comment on an excluded study (Kim 2008)
Lin 2014	Not a randomised controlled trial
Sakuramoto 2009	Not a randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Haverkamp 2015

Trial name or title	LOGICA
Methods	Randomised controlled trial
Participants	Early or advanced staged gastric adenocarcinoma
Interventions	Laparosopy-assisted versus open distal or total gastrectomy
Outcomes	Mortality, adverse events, health-related quality of life, length of hospital stay, clear resection margins, number of lymph nodes dissected, and long-term mortality
Starting date	December 2014
Contact information	R.vanHillegersberg@umcutrecht.nl
Notes	

Straatman 2015

Trial name or title	STOMACH
Methods	Randomised controlled trial
Participants	People with early or advanced gastric cancer receiving neoadjuvant chemotherapy
Interventions	Laparosopy-assisted versus open total gastrectomy
Outcomes	Mortality, health-related quality of life, length of hospital stay, number of lymph nodes dissected, and long-term mortality
Starting date	Not stated
Contact information	je.straatman@vumc.nl
Notes	

Yoshikawa 2012

Trial name or title	LANDSCOPE
Methods	Randomised controlled trial
Participants	People with advanced gastric cancer receiving neoadjuvant chemotherapy
Interventions	Laparosopy-assisted versus open distal gastrectomy
Outcomes	Mortality, adverse events, and long-term recurrence
Starting date	December 2014

Yoshikawa 2012 *(Continued)*

Contact information	yoshikawat@kcch.jp
Notes	

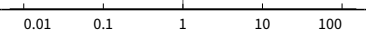
DATA AND ANALYSES

Comparison 1. Laparoscopic versus open gastrectomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term mortality	11	2335	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.50, 5.10]
2 Long-term mortality (maximal follow-up)	3	195	Hazard Ratio (Fixed, 95% CI)	0.94 [0.70, 1.25]
3 Proportion with a serious adverse event (< 3 months)	8	432	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.27, 1.34]
4 Short-term recurrence	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Long-term recurrence (maximal follow-up)	4		Hazard Ratio (Fixed, 95% CI)	Totals not selected
6 Proportion with an adverse event (< 3 months)	11	2490	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.01]
7 Proportion requiring blood transfusion during or within a week of surgery	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Quantity of perioperative blood transfused	2	143	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.27, 0.38]
9 Length of hospital stay	8	444	Mean Difference (IV, Random, 95% CI)	-1.38 [-2.57, -0.19]
10 Proportion with positive resection margins at histopathological examination	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11 Number of lymph nodes harvested	9	472	Mean Difference (IV, Fixed, 95% CI)	-0.63 [-1.51, 0.25]

Analysis 1.1. Comparison 1 Laparoscopic versus open gastrectomy, Outcome 1 Short-term mortality.

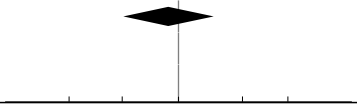
Study or subgroup	Laparoscopic gastrectomy n/N	Open gastrectomy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aoyama 2014	0/13	0/13			Not estimable
Cai 2011	0/49	0/47			Not estimable
Chen Hu 2012	0/41	0/44			Not estimable
Hayashi 2005	0/14	0/14			Not estimable
Hu 2015	2/308	0/299		11.05%	4.85[0.23,100.69]
Huscher 2005	1/30	2/29		44.29%	0.48[0.05,5.05]
Kim 2015	4/644	2/612		44.66%	1.9[0.35,10.34]
Kitano 2002	0/14	0/14			Not estimable
Lee 2005	0/24	0/23			Not estimable
Sakuramoto 2013	0/31	0/32			Not estimable
Takiguchi 2013	0/20	0/20			Not estimable
Total (95% CI)	**1188**	**1147**		**100%**	**1.6[0.5,5.1]**
Total events: 7 (Laparoscopic gastrectomy), 4 (Open gastrectomy)					
Heterogeneity: Tau^2=0; Chi^2=1.55, df=2(P=0.46); I^2=0%					
Test for overall effect: Z=0.79(P=0.43)					



Favours laparoscopic — Favours open

Analysis 1.2. Comparison 1 Laparoscopic versus open gastrectomy, Outcome 2 Long-term mortality (maximal follow-up).

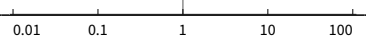
Study or subgroup	Laparoscopic gastrectomy N	Open gastrectomy N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
Cai 2011	49	47	-0 (0.35)		17.29%	0.96[0.48,1.91]
Huscher 2005	30	29	-0.1 (0.16)		82.71%	0.93[0.68,1.28]
Takiguchi 2013	20	20	0 (0)			Not estimable
Total (95% CI)					**100%**	**0.94[0.7,1.25]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.94); I^2=0%						
Test for overall effect: Z=0.45(P=0.66)						



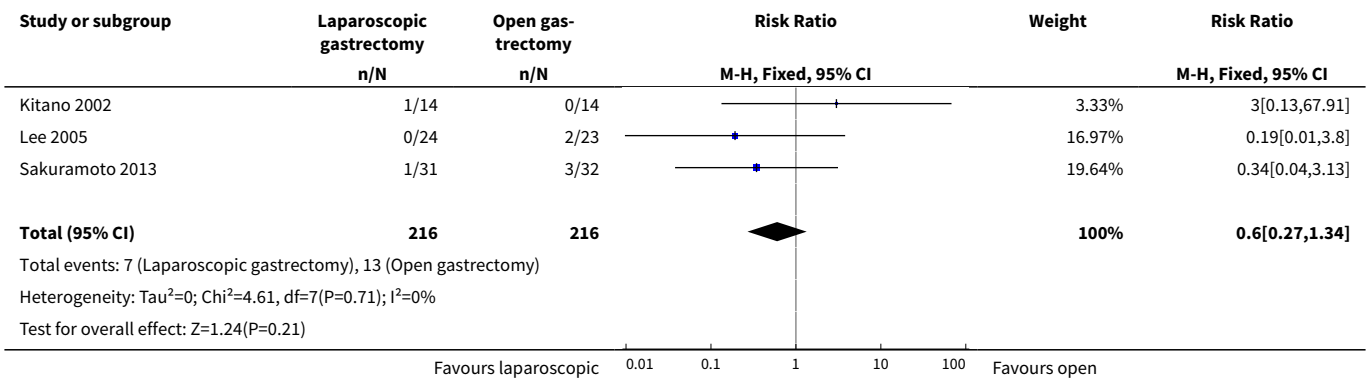
Favours laparoscopic — Favours open

Analysis 1.3. Comparison 1 Laparoscopic versus open gastrectomy, Outcome 3 Proportion with a serious adverse event (< 3 months).

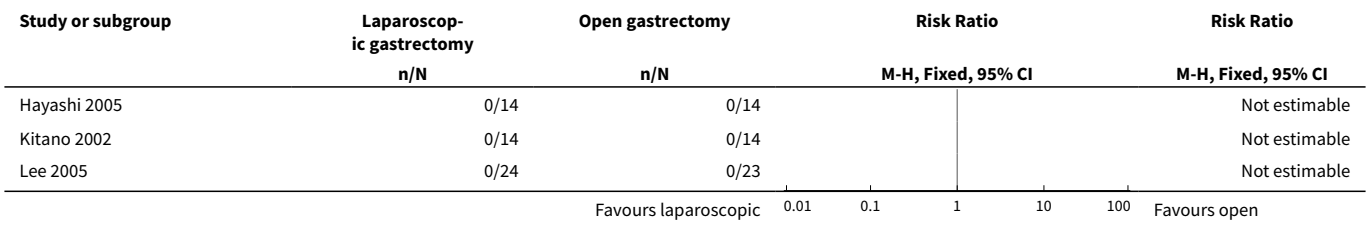
Study or subgroup	Laparoscopic gastrectomy n/N	Open gastrectomy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aoyama 2014	0/13	1/13		9.98%	0.33[0.01,7.5]
Cai 2011	1/49	0/47		3.39%	2.88[0.12,68.98]
Chen Hu 2012	2/41	1/44		6.42%	2.15[0.2,22.79]
Hayashi 2005	1/14	3/14		19.96%	0.33[0.04,2.83]
Huscher 2005	1/30	3/29		20.3%	0.32[0.04,2.92]



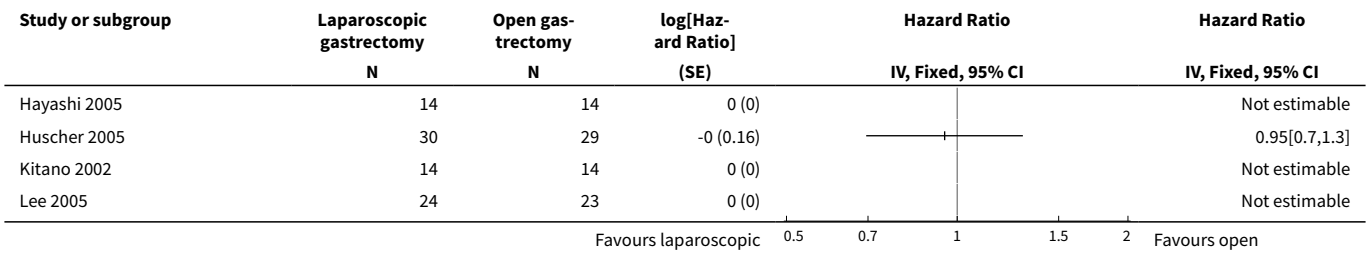
Favours laparoscopic — Favours open



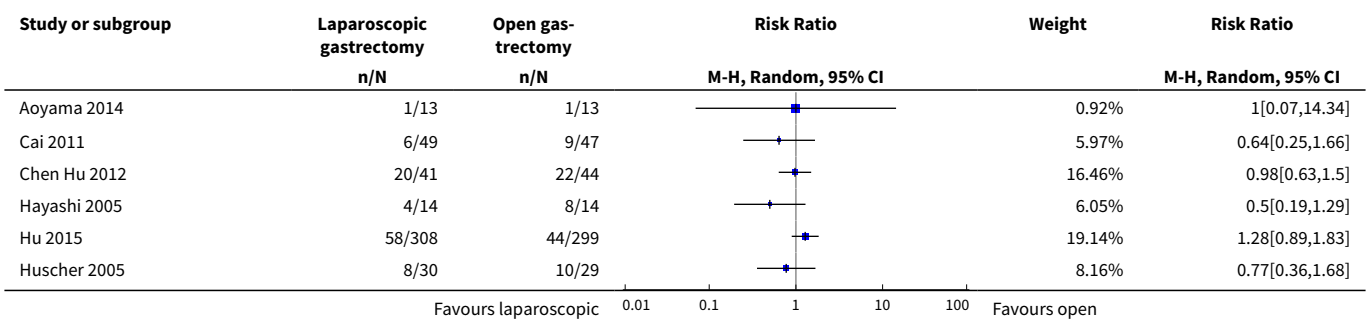
Analysis 1.4. Comparison 1 Laparoscopic versus open gastrectomy, Outcome 4 Short-term recurrence.

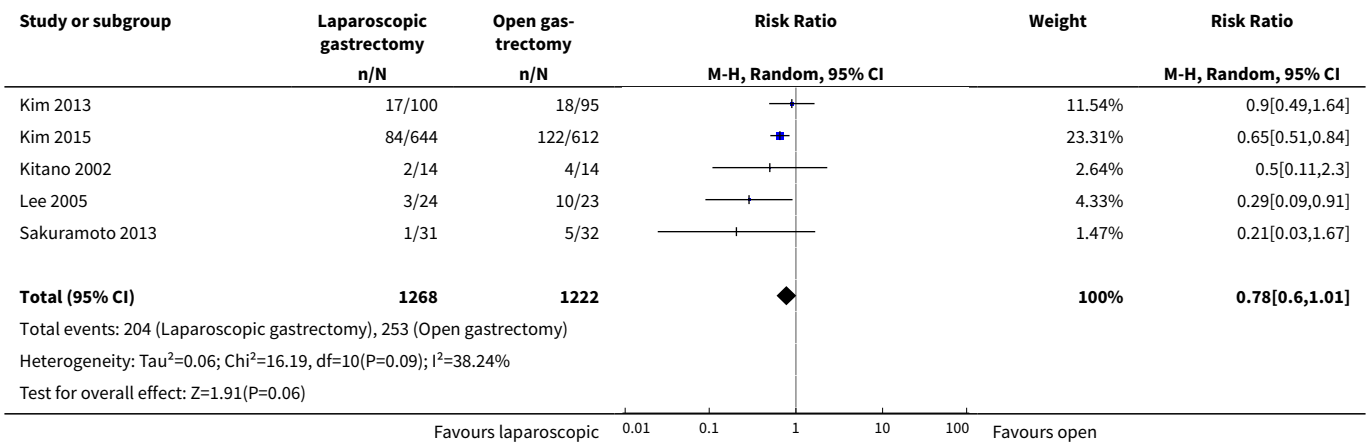


Analysis 1.5. Comparison 1 Laparoscopic versus open gastrectomy, Outcome 5 Long-term recurrence (maximal follow-up).

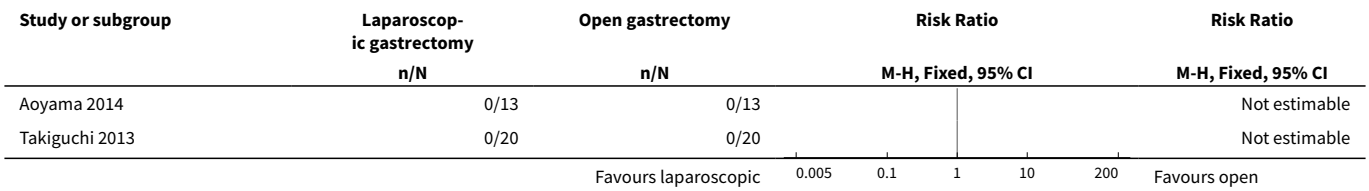


Analysis 1.6. Comparison 1 Laparoscopic versus open gastrectomy, Outcome 6 Proportion with an adverse event (< 3 months).

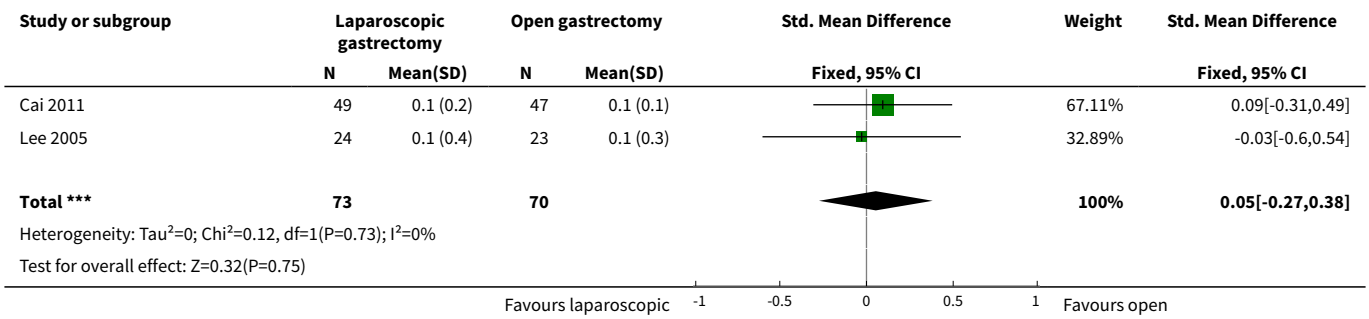




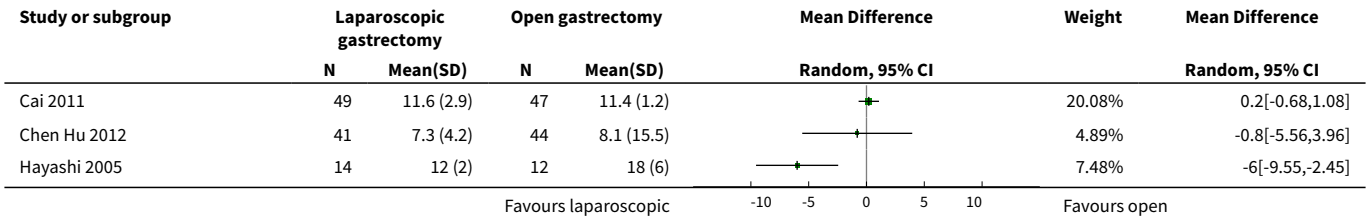
Analysis 1.7. Comparison 1 Laparoscopic versus open gastrectomy, Outcome 7 Proportion requiring blood transfusion during or within a week of surgery.



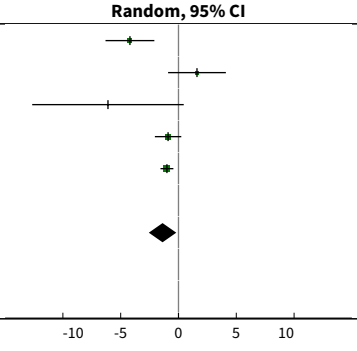
Analysis 1.8. Comparison 1 Laparoscopic versus open gastrectomy, Outcome 8 Quantity of perioperative blood transfused.



Analysis 1.9. Comparison 1 Laparoscopic versus open gastrectomy, Outcome 9 Length of hospital stay.



Study or subgroup	Laparoscopic gastrectomy		Open gastrectomy		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Huscher 2005	30	10.3 (3.6)	29	14.5 (4.6)		13.18%	-4.2[-6.31,-2.09]
Kitano 2002	14	17.6 (2.6)	14	16 (4)		11.3%	1.6[-0.9,4.1]
Lee 2005	24	11.2 (4.2)	23	17.3 (15.5)		2.87%	-6.1[-12.65,0.45]
Sakuramoto 2013	31	9.1 (1.1)	32	10 (3.1)		18.69%	-0.9[-2.04,0.24]
Takiguchi 2013	20	10 (0.9)	20	11 (0.9)		21.51%	-1[-1.56,-0.44]
Total * **	**223**		**221**			**100%**	**-1.38[-2.57,-0.19]**
Heterogeneity: Tau^2=1.63; Chi^2=29.62, df=7(P=0); I^2=76.37%							
Test for overall effect: Z=2.27(P=0.02)							



Analysis 1.10. Comparison 1 Laparoscopic versus open gastrectomy, Outcome 10 Proportion with positive resection margins at histopathological examination.

Study or subgroup	Laparoscopic gastrectomy	Open gastrectomy	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Kitano 2002	0/14	0/14		Not estimable

Analysis 1.11. Comparison 1 Laparoscopic versus open gastrectomy, Outcome 11 Number of lymph nodes harvested.

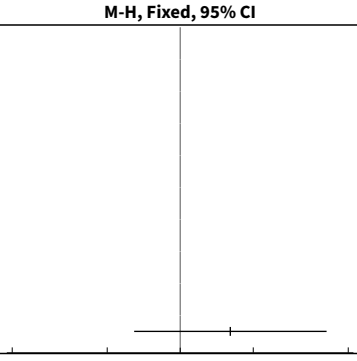
Study or subgroup	Laparoscopic gastrectomy		Open gastrectomy		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Aoyama 2014	13	40.5 (81.1)	13	43 (81.1)		0.02%	-2.5[-64.85,59.85]
Cai 2011	49	23 (2.7)	47	22.9 (2.4)		74.05%	0.1[-0.92,1.12]
Chen Hu 2012	41	18.3 (6.3)	44	19 (6.3)		10.74%	-0.7[-3.38,1.98]
Hayashi 2005	14	28 (14)	14	27 (10)		0.95%	1[-8.01,10.01]
Huscher 2005	30	30 (81.6)	29	33.4 (93.7)		0.04%	-3.4[-48.3,41.5]
Kitano 2002	14	20.2 (3.6)	14	24.9 (3.5)		11.16%	-4.7[-7.33,-2.07]
Lee 2005	24	31.8 (13.5)	23	38.1 (15.9)		1.08%	-6.3[-14.75,2.15]
Sakuramoto 2013	31	31.6 (12.2)	32	33.8 (13.4)		1.93%	-2.2[-8.52,4.12]
Takiguchi 2013	20	33 (81.6)	20	32 (93.7)		0.03%	1[-53.45,55.45]
Total * **	**236**		**236**			**100%**	**-0.63[-1.51,0.25]**
Heterogeneity: Tau^2=0; Chi^2=13.28, df=8(P=0.1); I^2=39.76%							
Test for overall effect: Z=1.4(P=0.16)							

Comparison 2. Laparoscopic versus open gastrectomy (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term mortality (stratified by early versus advanced cancer)	7		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Early gastric cancer	5		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Advanced gastric cancer	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Long-term mortality (maximal follow-up) (stratified by early versus advanced cancer)	2		Hazard Ratio (Fixed, 95% CI)	Totals not selected
2.1 Early gastric cancer	1		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Advanced gastric cancer	1		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Proportion with a serious adverse event (< 3 months) (stratified by early versus advanced cancer)	5	262	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.21, 1.60]
3.1 Early gastric cancer	4	166	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.14, 1.39]
3.2 Advanced gastric cancer	1	96	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [0.12, 68.98]
4 Short-term mortality (stratified by type of gastrectomy)	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Subtotal gastrectomy	10	2239	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.50, 5.10]
5 Long-term mortality (maximal follow-up) (stratified by type of gastrectomy)	2		Hazard Ratio (Fixed, 95% CI)	Totals not selected
5.1 Subtotal gastrectomy	2		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Proportion with a serious adverse event (< 3 months) (stratified by type of gastrectomy)	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Subtotal gastrectomy	7	336	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.22, 1.22]

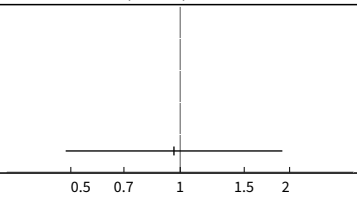
Analysis 2.1. Comparison 2 Laparoscopic versus open gastrectomy (subgroup analysis), Outcome 1 Short-term mortality (stratified by early versus advanced cancer).

Study or subgroup	Laparoscopic gastrectomy n/N	Open gastrectomy n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Early gastric cancer				
Hayashi 2005	0/14	0/14		Not estimable
Kitano 2002	0/14	0/14		Not estimable
Lee 2005	0/24	0/23		Not estimable
Sakuramoto 2013	0/31	0/32		Not estimable
Takiguchi 2013	0/20	0/20		Not estimable
2.1.2 Advanced gastric cancer				
Cai 2011	0/49	0/47		Not estimable
Hu 2015	2/308	0/299		4.85[0.23,100.69]



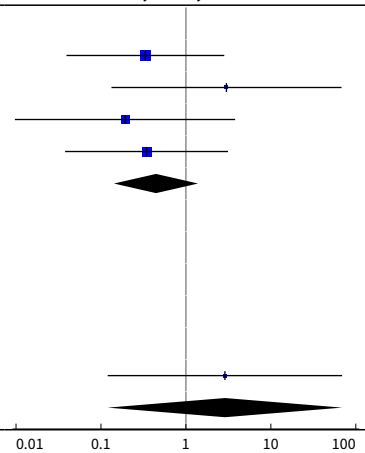
Analysis 2.2. Comparison 2 Laparoscopic versus open gastrectomy (subgroup analysis), Outcome 2 Long-term mortality (maximal follow-up) (stratified by early versus advanced cancer).

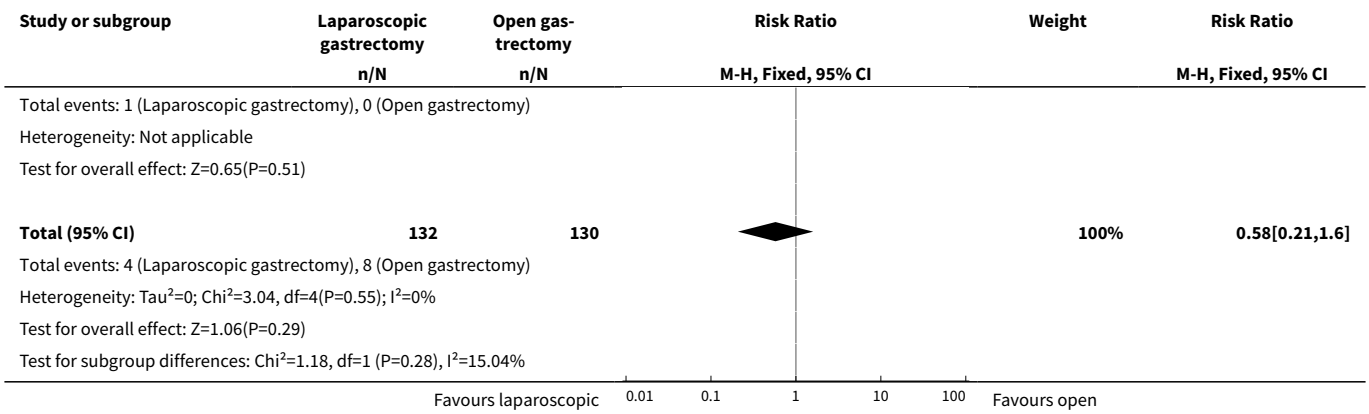
Study or subgroup	Laparoscopic gastrectomy N	Open gastrectomy N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
2.2.1 Early gastric cancer					
Takiguchi 2013	20	20	0 (0)		Not estimable
2.2.2 Advanced gastric cancer					
Cai 2011	49	47	-0 (0.35)		0.96[0.48,1.91]



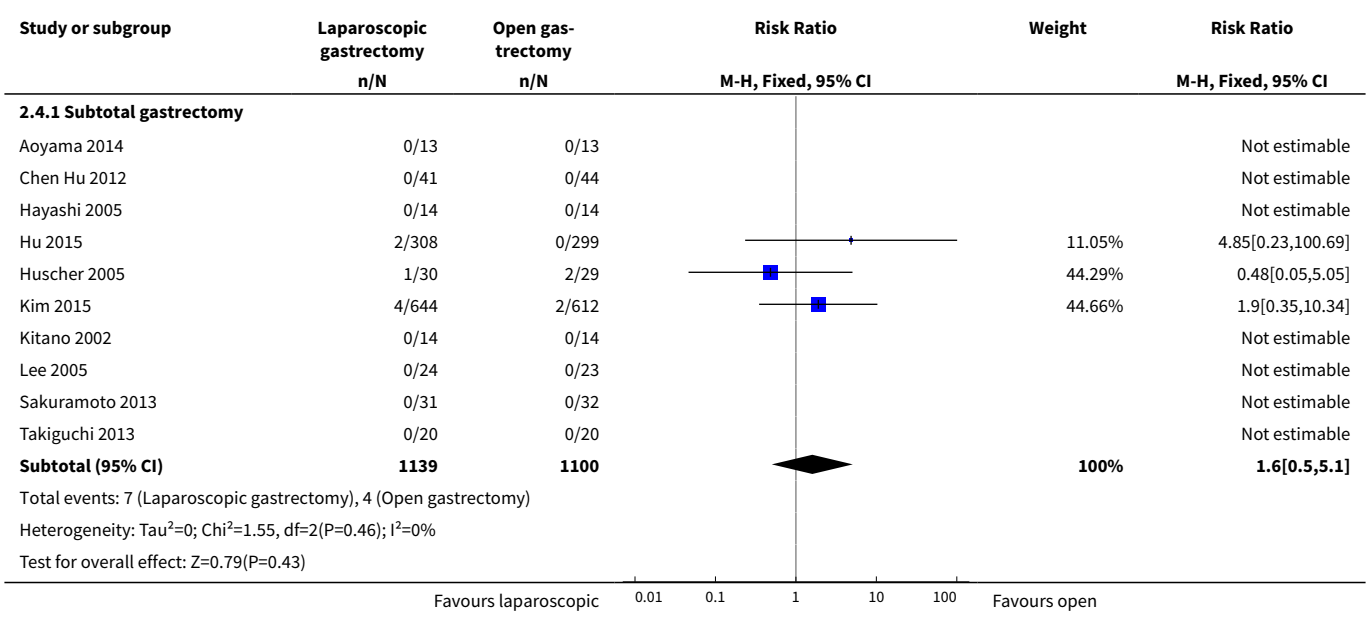
Analysis 2.3. Comparison 2 Laparoscopic versus open gastrectomy (subgroup analysis), Outcome 3 Proportion with a serious adverse event (< 3 months) (stratified by early versus advanced cancer).

Study or subgroup	Laparoscopic gastrectomy n/N	Open gastrectomy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Early gastric cancer					
Hayashi 2005	1/14	3/14		31.53%	0.33[0.04,2.83]
Kitano 2002	1/14	0/14		5.26%	3[0.13,67.91]
Lee 2005	0/24	2/23		26.81%	0.19[0.01,3.8]
Sakuramoto 2013	1/31	3/32		31.03%	0.34[0.04,3.13]
Subtotal (95% CI)	**83**	**83**		**94.64%**	**0.44[0.14,1.39]**
Total events: 3 (Laparoscopic gastrectomy), 8 (Open gastrectomy)					
Heterogeneity: Tau^2=0; Chi^2=1.86, df=3(P=0.6); I^2=0%					
Test for overall effect: Z=1.39(P=0.16)					
2.3.2 Advanced gastric cancer					
Cai 2011	1/49	0/47		5.36%	2.88[0.12,68.98]
Subtotal (95% CI)	**49**	**47**		**5.36%**	**2.88[0.12,68.98]**

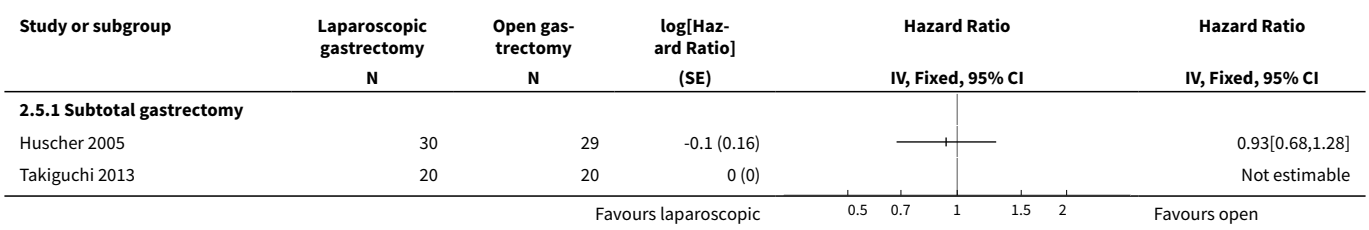




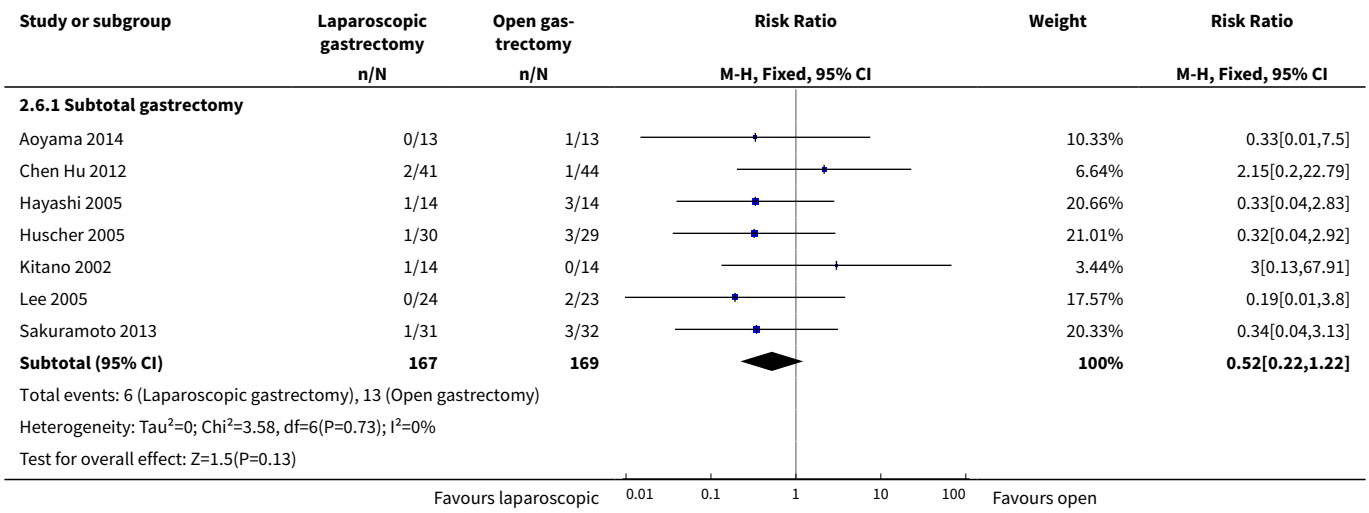
Analysis 2.4. Comparison 2 Laparoscopic versus open gastrectomy (subgroup analysis), Outcome 4 Short-term mortality (stratified by type of gastrectomy).



Analysis 2.5. Comparison 2 Laparoscopic versus open gastrectomy (subgroup analysis), Outcome 5 Long-term mortality (maximal follow-up) (stratified by type of gastrectomy).



Analysis 2.6. Comparison 2 Laparoscopic versus open gastrectomy (subgroup analysis), Outcome 6 Proportion with a serious adverse event (< 3 months) (stratified by type of gastrectomy).



APPENDICES

Appendix 1. CENTRAL search strategy

#1 (carcin* or cancer* or neoplas* or tumour* or tumor* or cyst* or growth* or adenocarcin* or malig*)

#2 (Intestin* or Digest* or Gastr* or gut or epigastr* or stomach* or abdomin*)

#3 #1 or #2

#4 MeSH descriptor: [Abdominal Neoplasms] explode all trees

#5 MeSH descriptor: [Intestinal Neoplasms] explode all trees

#6 MeSH descriptor: [Stomach Neoplasms] explode all trees

#7 #4 or #5 or #6

#8 #3 or #7

#9 (laparoscopy or laparoscopic)

#10 MeSH descriptor: [Laparoscopy] explode all trees

#11 #9 or #10

#12 gastrectomy

#13 MeSH descriptor: [Gastrectomy] explode all trees

#14 #12 or #13

#15 #8 and #11 and #14

Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. drug therapy.fs.

6. randomly.ab.

7. trial.ab.

8. groups.ab.

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. exp animals/ not humans.sh.

11. 9 not 10

12. (carcin* or cancer* or neoplas* or tumour* or tumor* or cyst* or growth* or adenocarcin* or malig*).mp.

13. (Intestin* or Digest* or Gastr* or gut or epigastr* or stomach*).mp.

14. 12 and 13

15. exp abdominal neoplasms/ or exp intestinal neoplasms/ or exp stomach neoplasms/

16. 14 or 15

17. (laparoscopy or laparoscopic).mp.

18. exp Laparoscopy/

19. 17 or 18

20. exp Gastrectomy/

21. gastrectomy.mp.

22. 20 or 21

23. 16 and 19 and 22

24. 11 and 23

Appendix 3. EMBASE search strategy

1. Clinical trial/

2. Randomized controlled trial/

3. Randomization/

4. Single-Blind Method/

5. Double-Blind Method/

6. Cross-Over Studies/

7. Random Allocation/

8. Placebo/

9. Randomi?ed controlled trial*.tw.

10. Rct.tw.

11. Random allocation.tw.

12. Randomly allocated.tw.

13. Allocated randomly.tw.

14. (allocated adj2 random).tw.

15. Single blind*.tw.

16. Double blind*.tw.

17. ((treble or triple) adj blind*).tw.

18. Placebo*.tw.

19. Prospective study/

20. or/1-19

21. Case study/

22. Case report.tw.

23. Abstract report/ or letter/

24. or/21-23

25. 20 not 24

26. (carcin* or cancer* or neoplas* or tumour* or tumor* or cyst* or growth* or adenocarcin* or malig*).mp.

27. exp neoplasm/ or exp tumor/

28. 26 or 27

29. (Intestin* or Digest* or Gastr* or gut or epigastr* or stomach*).mp.

30. 28 and 29

31. exp stomach tumor/ or exp abdominal tumor/ or exp stomach cancer/ or exp abdominal cancer/ or exp intestine cancer/ or exp stomach carcinoma/ or exp stomach carcinogenesis/ or exp stomach carcinoid/

32. 30 or 31

33. (laparoscopy or laparoscopic).mp.

34. exp laparoscopy/

35. 33 or 34

36. exp gastrectomy Billroth I/ or exp gastrectomy/ or exp partial gastrectomy/ or exp gastrectomy Billroth II/

37. gastrectomy.mp.

38. 36 or 37

39. 32 and 35 and 38

40. 25 and 39

Appendix 4. Science Citation Index search strategy

#1 TS=(carcin* or cancer* or neoplas* or tumour* or tumor* or cyst* or growth* or adenocarcin* or malig*)

#2 TS=(Intestin* or Digest* or Gastr* or gut or epigastr* or stomach*)

#3 TS=(laparoscopy or laparoscopic)

#4 TS=(gastrectomy)

#5 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*)

#6 #5 AND #4 AND #3 AND #2 AND #1

Appendix 5. ClinicalTrials.gov search strategy

"Interventional" [STUDY-TYPES] AND gastrectomy [DISEASE] AND (laparoscopy OR laparoscopic) [TREATMENT] AND ("Phase 2" OR "Phase 3" OR "Phase 4") [PHASE]

Appendix 6. WHO ICTRP search strategy

Gastrectomy AND laparoscop*

WHAT'S NEW

Date	Event	Description
31 March 2016	Amended	The results section of the abstract was amended to correct a typographic error calculating 7/1188 as 6% rather than 0.6%.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: KG.
Designing the review: KG, MM.
Co-ordinating the review: KG.
Designing search strategies: KG.
Writing the review: LB, KG.
Providing general advice on the review: MM.
Securing funding for the review: KG.
Performing previous work that was the foundation of the current study: KG.

DECLARATIONS OF INTEREST

This report is independent research, funded by the National Institute for Health Research (NIHR Cochrane Programme Grants, 13/89/03 - Evidence-based diagnosis and management of upper digestive, hepato-biliary, and pancreatic disorders). The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service (NHS), the National Institute for Health Research, or the Department of Health.

LMJB: none known.

MM: none known.

KSG: none known.

SOURCES OF SUPPORT

Internal sources

- University College London, UK.

External sources

- National Institute for Health Research, UK.

  This report is independent research, funded by the National Institute for Health Research (NIHR Cochrane Programme Grants, 13/89/03 - Evidence-based diagnosis and management of upper digestive, hepato-biliary, and pancreatic disorders). The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service (NHS), the National Institute for Health Research, or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The search strategy was revised after the protocol was published as it was not sufficiently sensitive to identify known trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Gastrectomy [adverse effects] [*methods] [mortality]; Laparoscopy [adverse effects] [*methods] [mortality]; Stomach Neoplasms [mortality] [*surgery]

MeSH check words

Humans